IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC.,	)	
	)	
Plaintiff,	)	
	)	C.A. No. 18-956 (MSG)
v.	)	
	)	
ACCORD HEALTHCARE, INC.,	)	
	)	
Defendant.	)	

DECLARATION OF JOSHUA I. ROTHMAN IN SUPPORT OF PLAINTIFF'S OPENING CLAIM CONSTRUCTION BRIEF

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June 28, 2019

I, Joshua I. Rothman, an attorney duly admitted to practice law in the State of New York, hereby declare that the following is true to the best of my knowledge:

1. I am a Partner at Venable LLP (formerly Fitzpatrick, Cella, Harper & Scinto), 1290 Avenue of the Americas, New York, New York 10104, and counsel for Plaintiff Amgen Inc. ("Amgen") in the instant action. I am fully familiar with the facts and circumstances of this matter.

2. I submit this declaration in support of Amgen's Opening Claim Construction Brief.

3. Attached hereto as Exhibit 1 is a true and correct copy of U.S. Patent No. 9,375,405.

4. Attached hereto as Exhibit 2 is a true and correct copy of PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN, 366-368, 406-408, Michael E. Aulton ed. (2nd ed. 2002).

5. Attached hereto as Exhibit 3 is a true and correct copy of HANDBOOK OF PHARMACEUTICAL EXCIPIENTS, Raymond C. Rowe et al. eds., 118-121, 129-133, 317-322, 326-329, 581-585. 691-694 (6th ed. 2009).

6. Attached hereto as Exhibit 4 is a true and correct copy of REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, Alfonso R. Gennaro ed., 1032 (20th ed. 2000).

7. Attached hereto as Exhibit 5 is a true and correct copy of the December 10, 2015 Notice of Allowability with Bates Range Numbers SENS-AMG00001587-1596.

8. Attached hereto as Exhibit 6 is a true and correct copy of the October 18, 2015 Notice of Allowability with Bates Range Numbers SENS-AMG00001064-1070.

9. Attached hereto as Exhibit 7 is a true and correct copy of the April 6, 2016 Notice of Allowability with Bates Range Numbers SENS-AMG00001643-1650.

Dated: June 28, 2019

By: /s/ Joshua I. Rothman
Joshua I. Rothman

EXHIBIT 1

U 7629975

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

April 06, 2017

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *9,375,405*
ISSUE DATE: *June 28, 2016*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

R GLOVER
Certifying Officer


US009375405B2

(12) **United States Patent**
Lawrence et al.

(10) **Patent No.: US 9,375,405 B2**
(45) **Date of Patent: *Jun. 28, 2016**

(54) **RAPID DISSOLUTION FORMULATION OF A CALCIUM RECEPTOR-ACTIVE COMPOUND**

(75) Inventors: **Glen Gary Lawrence**, Thousand Oaks, CA (US); **Francisco J. Alvarez**, Newbury Park, CA (US); **Hung-Ren H. Lin**, Oak Park, CA (US); **Tzuchi R. Ju**, Vernon Hills, IL (US)

(73) Assignee: **Amgen, Inc.**, Thousand Oaks, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1190 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/942,646**

(22) Filed: **Nov. 9, 2010**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 10/937,870, filed on Sep. 10, 2004, now Pat. No. 7,829,595.

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(51) **Int. Cl.**

A61K 31/135	(2006.01)
A61K 31/137	(2006.01)
A61K 31/00	(2006.01)
A61K 9/20	(2006.01)
A61K 9/28	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/00*** (2013.01); ***A61K 9/2077*** (2013.01); ***A61K 31/135*** (2013.01); ***A61K 31/137*** (2013.01); *A61K 9/2866* (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/135; A61K 31/137

USPC 514/275, 579, 607, 614, 646, 649; 424/434, 464, 465, 476, 490

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient, wherein the composition has a controlled dissolution profile. The present invention further relates to a method of manufacturing the pharmaceutical composition, as well as a method of treating a disease using the pharmaceutical composition.

23 Claims, 1 Drawing Sheet

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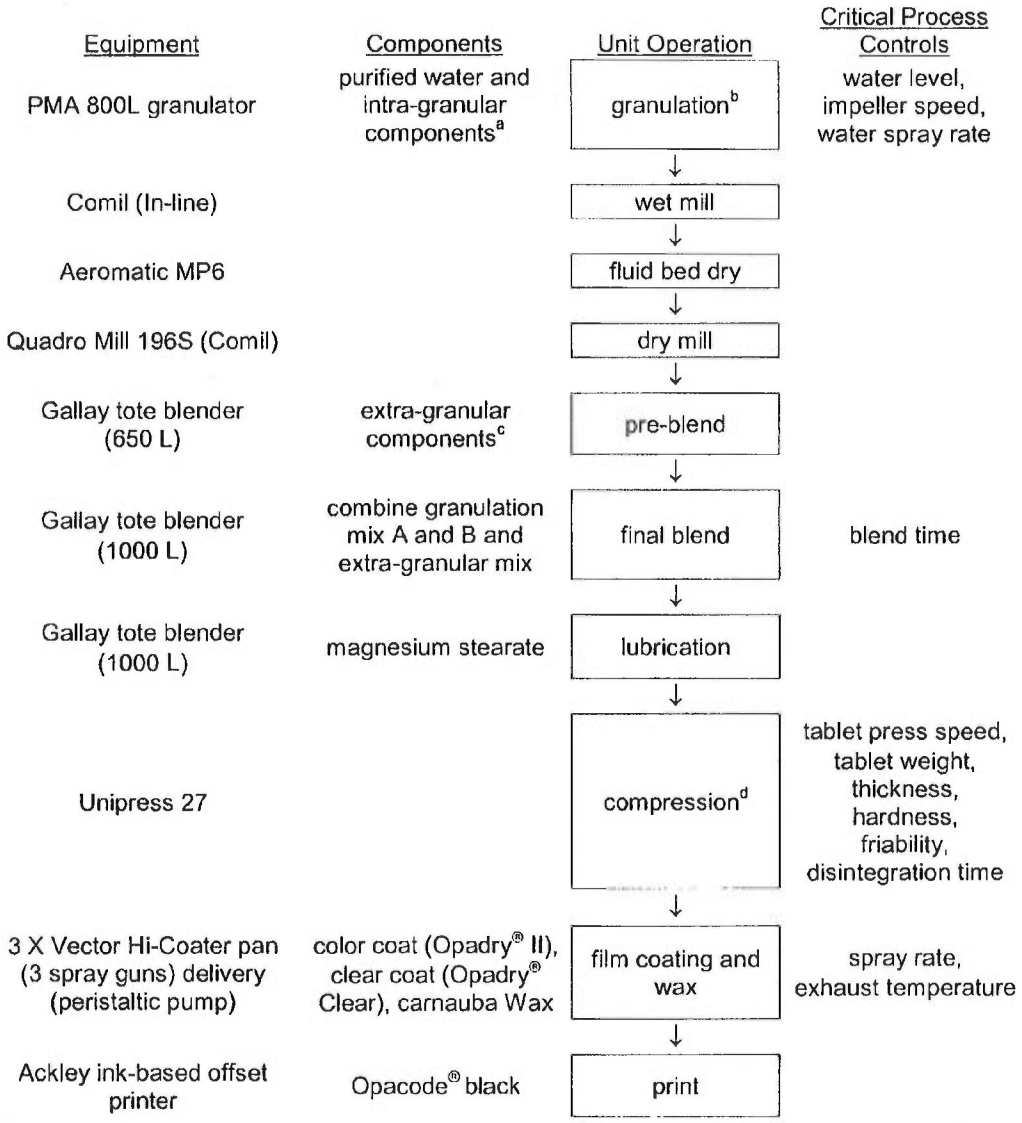


[a] cinacalcet HCl, pregelatinized starch, microcrystalline cellulose, povidone, and crospovidone

[b] The granulation step to dry milling step is repeated to generate 2 bowls of wet granulation (Mix A and B).

[c] Extra-granular components are microcrystalline cellulose, crospovidone, and colloidal silicon dioxide

[d] Tooling dimension is dependent on tablet size and strength, (30 mg; 0.2372" x 0.3800" oval shape plain, 60 mg; 0.3000" x 0.4800" modified oval (double radius) plain, 90 mg; 0.3420" x 0.5480" modified oval (double radius) plain)

RAPID DISSOLUTION FORMULATION OF A CALCIUM RECEPTOR-ACTIVE COMPOUND

This application claims the benefit of priority of U.S. Provisional Patent Application No. 60/502,219, filed Sep. 12, 2003.

Calcium receptor-active compounds are known in the art. One example of a calcium receptor-active compound is cinacalcet HCl, which is described, for example, in U.S. Pat. No. 6,001,884. Such calcium receptor-active compounds may be insoluble or sparingly soluble in water, particularly in their non-ionized state. For example, cinacalcet has a solubility in water of less than about 1 μg/mL at neutral pH. The solubility of cinacalcet can reach about 1.6 mg/mL when the pH ranges from about 3 to about 5. However, when the pH is about 1, the solubility decreases to about 0.1 mg/mL. Such limited solubility can reduce the number of formulation and delivery options available for these calcium receptor-active compounds. Limited water solubility can also result in low bioavailability of the compounds.

There is therefore a need to maximize the dissolution of the calcium receptor-active compound from a dosage form, and potentially during in vivo exposure. There is also a need to improve the bioavailability of the calcium receptor-active compound during in vivo exposure.

One aspect of the present invention provides a pharmaceutical composition comprising at least one calcium receptor active compound in combination with at least one pharmaceutically acceptable carrier. Certain embodiments of the present invention are directed to a pharmaceutical composition with a defined dissolution profile.

The invention also provides a method of manufacturing the pharmaceutical composition to achieve the desired dissolution profile, as well as a method of treating a disease using the pharmaceutical composition. In addition, certain embodiments of the present invention are directed to a method for controlling dissolution rate of a formulation comprising the pharmaceutical composition.

According to one aspect of the invention, the invention provides a pharmaceutical composition comprising an effective dosage amount of at least one calcium receptor-active compound and at least one pharmaceutically acceptable excipient, wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in United States Pharmacopeia (USP)—National Formulary (NF) (USP 26/NF 21), chapter 711 using a USP 2 apparatus at a temperature of 37° C.±0.5° C., and at a rotation speed of 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

According to another aspect of the invention, the invention provides a pharmaceutical composition comprising an effective dosage amount of at least one calcium receptor-active compound and at least one pharmaceutically acceptable excipient, wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in USP 26/NF 21, chapter 711 using a USP 2 apparatus at a temperature of about 37° C., and at a rotation speed of about 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

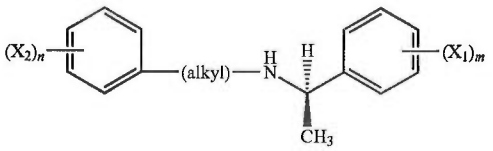
The invention also provides a method of controlling the dissolution rate of a formulation comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient, the method

comprising producing the formulation in a granulator which has a volume ranging from about 1 L to about 2000 L, and contains water in a granulation level ranging from about 10% to about 50% relative to the weight of the dry powders in the granulator.

The calcium receptor-active compound useful in the claimed invention may be a calcimimetic compound or a calcilytic compound. As used herein, the term "calcimimetic compounds" refers to compounds that bind to a calcium receptor, and induce a conformational change that reduces the threshold for calcium receptor activation by the endogenous ligand Ca^{2+}, thereby reducing parathyroid hormone ("PTH") secretion. These calcimimetic compounds can also be considered allosteric modulators of the calcium receptor. As used herein, the term "calcilytic compounds" refers to compounds that act as calcium receptor antagonists, and stimulate PTH secretion.

The calcimimetic compounds and calcilytic compounds useful in the present invention include those disclosed in, for example, European Patent No. 933 354; International Publication Nos. WO 01/34562, WO 93/04373, WO 94/18959, WO 95/11221, WO 96/12697, WO 97/41090; U.S. Pat. Nos. 5,981,599, 6,001,884, 6,011,068, 6,031,003, 6,172,091, 6,211,244, 6,313,146, 6,342,532, 6,363,231, 6,432,656, and U.S. Patent Application Publication No. 2002/0107406. The calcimimetic compounds and/or calcilytic compounds disclosed in these patents and published applications are incorporated herein by reference.

In certain embodiments, the calcium receptor-active compounds are chosen from compounds of formula (I) and pharmaceutically acceptable salts thereof



(I)

wherein:

X_1 and X_2, which may be identical or different, are each a radical chosen from CH_3, CH_3O, CH_3CH_2O, Br, Cl, F, CF_3, CHF_2, CH_2F, CF_3O, CH_3S, OH, CH_2OH, $CONH_2$, CN, NO_2, CH_3CH_2, propyl, isopropyl, butyl, isobutyl, t-butyl, acetoxy, and acetyl radicals, or two of X_1 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical, or two of X_2 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical; provided that X_2 is not a 3-t-butyl radical;

n ranges from 0 to 5;

m ranges from 1 to 5; and

the alkyl radical is chosen from C1-C3 alkyl radicals, which are optionally substituted with at least one group chosen from saturated and unsaturated, linear, branched, and cyclic C1-C9 alkyl groups, dihydroindolyl and thiodihydroindolyl groups, and 2-, 3-, and 4-piperid(in)yl groups; and the stereoisomers thereof.

Calcium receptor-active compounds useful in the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate,

glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, mandelate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 2-phenylpropionate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate, mesylate, and undecanoate. When compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable salts for the carboxy group are well known to those skilled in the art and include, for example, alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. For additional examples of "pharmacologically acceptable salts," see infra and Berge et al., *J. Pharm. Sci.* 66:1 (1977). In certain embodiments of the invention salts of hydrochloride and salts of methanesulfonic acid can be used.

In some embodiments of the present invention, the calcium-receptor active compound can be chosen from cinacalcet, i.e., N-(1-(R)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl) phenyl]-1-aminopropane, cinacalcet HCl, and cinacalcet methanesulfonate. The cinacalcet HCl and cinacalcet methanesulfonate can be in various forms, such as amorphous powders, crystalline powders, and mixtures thereof. For example, the crystalline powders can be in forms including polymorphs, psuedopolymorphs, crystal habits, micromeretics, and particle morphology.

The therapeutically effective amount of the calcium receptor-active compound in the compositions disclosed herein ranges from about 1 mg to about 360 mg, for example from about 5 mg to about 240 mg, or from about 20 mg to about 100 mg. As used herein, the "therapeutically effective amount" is an amount that changes in a desired manner at least one of the calcium level, the phosphorus level, the PTH level, and the calcium phosphorus product in a subject. In some embodiments, the therapeutically effective amount of cinacalcet HCl in the composition disclosed herein can be chosen from about 5 mg, about 15 mg, about 30 mg, about 50 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 210 mg, about 240 mg, about 300 mg, or about 360 mg.

While it may be possible to administer a compound of the invention alone, the compound administered will normally be present as an active ingredient in a pharmaceutical composition. Thus, a pharmaceutical composition of the invention may comprise a therapeutically effective amount of at least one calcium receptor-active compound, or an effective dosage amount of at least one calcium receptor-active compound.

As used herein, an "effective dosage amount" is an amount that provides a therapeutically effective amount of the at least one calcium receptor active compound when provided as a single dose, in multiple doses, or as a partial dose. Thus, an effective dosage amount of the at least one calcium receptor active compound of the invention includes an amount less than, equal to or greater than an effective amount of the compound; for example, a pharmaceutical composition in which two or more unit dosages, such as in tablets, capsules and the like, are required to administer an effective amount of the compound, or alternatively, a multidose pharmaceutical composition, such as powders, liquids and the like, in which an effective amount of the at least one calcium receptor-active compound is administered by administering a portion of the composition.

Alternatively, a pharmaceutical composition in which two or more unit dosages, such as in tablets, capsules and the like, are required to administer an effective amount of the at least one calcium receptor active compound may be administered in less than an effective amount for one or more periods of time (i.e., a once-a-day administration, and a twice-a-day administration), for example to ascertain the effective dose for an individual subject, to desensitize an individual subject to potential side effects, to permit effective dosing readjustment or depletion of one or more other therapeutics administered to an individual subject, and/or the like.

The effective dosage amount of the pharmaceutical composition disclosed herein ranges from about 1 mg to about 360 mg from a unit dosage form, for example about 5 mg, about 15 mg, about 30 mg, about 50 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 210 mg, about 240 mg, about 300 mg, or about 360 mg from a unit dosage form.

In some embodiments of the present invention, the compositions disclosed herein comprise a therapeutically effective amount of cinacalcet HCl for the treatment of hyperparathyroidism, such as primary hyperparathyroidism and secondary hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium-phosphorus product. For example, in certain embodiments, the cinacalcet HCl can be present in an amount ranging from about 1% to about 70%, such as from about 5% to about 40%, from about 10% to about 30%, or from about 15% to about 20%, by weight relative to the total weight of the composition.

The compositions of the invention may contain one or more active ingredients in addition to the calcium receptor-active compound. The additional active ingredient may be another calcium receptor-active compound, or it may be an active ingredient having a different therapeutic activity. Examples of such additional active ingredients include, for example, vitamins and their analogs, such as vitamin D and analogs thereof, antibiotics, and cardiovascular agents.

The cinacalcet HCl or other calcium receptor-active compound that can be used in the composition is typically present in the form of particles. These particles can have a particle D_{50} of, for example, less than or equal to about 50 μm. As used herein, the "particle D_{50}" is the particle size of the active pharmaceutical ingredient at the 50^{th} percentile of a particle size distribution. According to certain embodiments of the invention, the active pharmaceutical ingredient in the formulation has a particle D_{50} that is less than the granule D_{50} of the formulation, discussed in detail below.

The particle D_{50} of the cinacalcet HCl particles can be determined by one of ordinary skill in the art using known light scattering techniques. In one embodiment of the invention, the particle D_{50} of the cinacalcet HCl particles is determined by using a particle size analyzer, such as a Malvern Mastersizer analyzer, that uses a laser to scan a suspension of particles. The particles diffract the incoming light to detectors: smaller particles diffract light at larger angles, while larger particles diffract light at smaller angles. The light intensities observed at each detector are translated into a particle size distribution based on the diameter of a sphere that has an equivalent volume to that of the measured particles.

Specifically, the particle size distribution of the active pharmaceutical ingredient, for example, cinacalcet HCl, can be determined according to the following procedure. The following instrument conditions in a Malvern Mastersizer particle size analyzer are specified in its software:

Refractive Index Sample	1.630
Absorptive Index	0.1
Refractive Index Dispersant	1.375
Analysis model	General purpose spherical
Calculation sensitivity	Enhanced

-continued

Measurement snaps and time	20,000 snaps over 20 seconds
Background snaps and time	20,000 snaps over 20 seconds
Stir speed	1750 rpm

While stirring, about 170 mL of a dispersion of about 0.1% sorbitan trioleate (for example Span 85®, available from Kishida Chemical) in hexane ("dispersant-B"), is added to the sampling unit, and the laser is aligned to take a background measurement of the dispersant-B.

The entire suspension containing the cinacalcet HCl is added until a suitable obscuration range ranging from about 10 to about 20% is obtained. The sample is measured after the obscuration value has stabilized. After the measurement, the system is drained and rinsed once with about 170 mL of dispersant-B, the dispersant-B is drained, and the sampling unit is refilled with about 170 mL of dispersant-B. The measurement are repeated two more times with different riffled fractions. The riffling is performed on large samples to obtain small representative particle size fractions about 15 mg in size.

The Obscuration, D(v,0.1), D(v,0.5), D(v,0.9) values are then calculated from these measurements. The average, standard deviation, and relative standard deviation (RSD) of the D(v,0.1), D(v,0.5), D(v,0.9) values is also calculated. The RSD (%) is calculated as follows:

$$RSD\ (\%) = \frac{100}{\overline{X}}\left[\frac{\sum_{i=1}^{N}(X_i - \overline{X})^2}{N-1}\right]^{\frac{1}{2}}$$

where X, is an individual measurement in a set of N measurements and is the arithmetic mean of the set.

The composition disclosed herein can be in various forms, for example, in granular form. The granules that can be used in the present invention can have a granule D_{50} ranging from about 50 μm to about 150 μm, such as from about 80 μm to about 130 μm. As defined herein, the "granule D_{50}" is the particle size of the composition at the 50^{th} percentile of a particle size distribution. The granule D_{50} can readily be determined by one of ordinary skill in the art using sieve analysis techniques. Specifically, the granule D_{50} is determined according to the following procedure.

Approximately 100 g of sample is added to sieve shaker equipped with 40 mesh, 60 mesh, 80 mesh, 100 mesh, 140 mesh, 200 mesh, 325 mesh, and the bottom pan. The sieve shaker is then turned on for about 10 minutes to separate the sample according to particle size. Each sieve is weighed to determine the amount of sample retained on each sieve and the bottom pan. The individual sieve weight is normalized to generate sieve weight fraction. The individual sieve weight fraction is calculated by dividing each sieve weight with the sum of all sieve weights.

$$\text{Weight Fraction of each sieve} = \frac{\text{Weight of each sieve}}{\text{Sum of all sieves}}$$

Before the particle size calculation, the mean size range must be determined for each sieve and the bottom pan. This mean size of each sieve screen represents the mean particle size retained on the screen. The mean size of each sieve screen

is determined by the hole size of the screen (lower limit) and one sieve size larger (upper limit). In the case of the 40 mesh sieve screen, the hole size of about 1410 μm is used as an upper limit. Table 1 set forth below shows the particle size range of any retained material on each screen and the mean of the particle size range.

TABLE 1

Screens	Hole size of each screen (μm)	Particle size range of retained material on each screen (μm)	Median particle size of the screen (μm)
40 mesh	425	425-1410	918
60 mesh	250	250-424	337
80 mesh	180	180-249	215
100 mesh	150	150-179	165
140 mesh	106	106-149	128
200 mesh	75	75-105	90
325 mesh	45	45-74	60
Bottom pan	0	1-44	23

The weight fraction of each sieve is added to generate cumulative frequency distribution starting from the bottom pan to 40 mesh screen. Once the cumulative frequency distribution is generated, the corresponding particle size at 10 percentile (D_{10}), 50-percentile (D_{50}), and 90-percentile (D_{90}) are determined. The particle size of the corresponding percentile is determined by linear interpolation between two consecutive data from the cumulative frequency distribution. For example, particle size of 50-percentile (D_{50}) is interpolated by,

$$D_{50}(\mu m) = \frac{[(50 - X_n) * d_{n+1} + (X_{n+1} - 50) * d_n]}{(X_{n+1} - X_n)}$$

where,

X_n=cumulative quantity of sample that is just below 50-percentile (in %);

d_n=mean of the particle size range from the sieve screen where X_n occurs (in mm);

X_{n+1}=next cumulative quantity of sample that is above 50-percentile (in %).

d_{n+1}=mean of the particle size range from the sieve screen where X_{n+1} occurs (in mm).

According to all embodiments of the present invention, the particle size of active pharmaceutical ingredient is measured according to light scattering techniques, and the particle size of the granules of composition is measured according to sieve analysis.

The compositions disclosed herein can be in a form chosen from, for example, tablets, capsules, and powders. The tablets can be made by pressing the granules into the form of tablets. The capsules can also be made using the granules.

The at least one pharmaceutically acceptable excipient can be chosen from, for example, diluents such as starch, microcrystalline cellulose, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins; binders such as povidone, hydroxypropyl methylcellulose, dihydroxy propylcellulose, and sodium carboxyl methylcellulose; and disintegrants such as crospovidone, sodium starch glycolate, croscarmellose sodium, and mixtures of any of the foregoing. The at least one pharmaceutically acceptable excipient can further be chosen from lubricants such as magnesium stearate, calcium stearate, stearic acid, glyceryl behenate, hygrogenated vegetable oil,

glycerine fumarate and glidants such as colloidal silicon dioxide, and mixtures thereof. In some embodiments of the present invention, the at least one pharmaceutically acceptable excipient is chosen from microcrystalline cellulose, starch, talc, povidone, crospovidone, magnesium stearate, colloidal silicon dioxide, sodium dodecyl sulfate, and mixtures of any of the foregoing. The excipients of the present invention, can be intragranular, intergranular, or mixtures thereof.

In some embodiments of the present invention, the composition and/or the granules within the composition can comprise microcrystalline cellulose and starch in a weight ratio ranging from about 1:1 to about 15:1. For example, in the composition, the weight ratio of the microcrystalline cellulose and starch can range from about 1:1 to about 15:1, such as about 10:1, and in the granules within the composition, the weight ratio of the microcrystalline cellulose and starch can range from about 1:1 to about 10:1, such as about 5:1.

The microcrystalline cellulose can be present in an amount ranging from about 25% to about 85%, for example from about 50% to about 80%, or from about 60% to about 75% by weight relative to the total weight of the composition. The starch can be present in an amount ranging from about 5% to about 35%, for example, from about 5% to about 25%, or from about 5% to about 10% by weight relative to the total weight of the composition.

The compositions disclosed herein can further comprise at least one ingredient chosen from coating materials that are known in the art such as, for example, hydroxypropyl methylcellulose.

Certain compositions can comprise:

(a) from about 10% to about 40% by weight of a calcium receptor-active compound chosen from cinacalcet HCl and cinacalcet methanesulfonate;

(b) from about 45% to about 85% by weight of at least one diluent;

(c) from about 1% to about 5% by weight of at least one binder; and

(d) from about 1% to about 10% by weight of at least one disintegrant;

wherein the percentage by weight is relative to the total weight of the composition. The compositions can further comprise from about 0.05% to about 5% by weight, relative to the total weight of the composition, of at least one additive chosen from glidants, lubricants, and adherents. The composition can additionally comprise from about 1% to about 6% by weight of at least one coating material, relative to the total weight of the composition.

In another embodiment, the composition disclosed herein comprises:

(a) from about 10% to about 40% by weight of cinacalcet HCl;

(b) from about 5% to about 10% by weight of starch;

(c) from about 40% to about 75% by weight of microcrystalline cellulose;

(d) from about 1% to about 5% by weight of povidone; and

(e) from about 1% to about 10% by weight of crospovidone;

wherein the percentage by weight is relative to the total weight of the composition.

The povidone can be present in an amount ranging from about 1% to about 5%, for example, from about 1% to about 3% by weight relative to the total weight of the composition. The crospovidone can be present in an amount ranging from about 1% to about 10%, for example from about 3% to about 6%, by weight relative to the total weight of the composition.

The composition can further comprise from about 0.05% to about 5% by weight, relative to the total weight of the composition, of at least one additive chosen from colloidal silicon dioxide, magnesium stearate, talc, and the like, and mixtures of any of the foregoing. In certain embodiments of the invention, the composition comprises from about 0.05% to about 1.5% of colloidal silicon dioxide, from about 0.05% to about 1.5% of magnesium stearate, from about 0.05% to about 1.5% of talc, or mixtures of any of the foregoing. The composition can even further comprise from about 1% to about 6% by weight of at least one coating material, relative to the total weight of the composition.

As mentioned above, the compositions of certain embodiments of the present invention have a dissolution profile that results in about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition no later that about 30 minutes from the start of a dissolution test that is conducted in 0.05 N HCl in a U.S.P. 2 apparatus at a temperature of 37° C.±0.5° C. at a rotation speed of 75 r.p.m. The dissolution test is conducted using a USP 2 apparatus, and according to the dissolution protocol described in USP 26/NF 21, chapter 711, which is incorporated herein by reference. According to this embodiment using this dissolution protocol, a stated volume of the dissolution medium (±1%) is placed in the vessel of the USP 2 apparatus, the apparatus is assembled, the dissolution medium is equilibrated to 37° C.±0.5° C., the thermometer is removed, the dosage form is placed in the vessel, and the amount of active pharmaceutical ingredient that is released as a function of time is measured.

According to another embodiment of the invention, a stated volume of the dissolution medium is placed in the vessel of the USP 2 apparatus, the apparatus is assembled, the dissolution medium is equilibrated to about 37° C., the thermometer is removed, the dosage form is placed in the vessel, and the amount of active pharmaceutical ingredient that is released as a function of time is measured.

The dissolution profile represents the percentage of the active pharmaceutical ingredient released based on a target amount of the active pharmaceutical ingredient in the formulation. As used herein "target amount" refers to the amount of active pharmaceutical ingredient in each formulation. In certain embodiments, the target amount refers to the label amount and/or label claim.

USP 26/NF 21, chapter 905, defines a protocol used to determine the dosage-unit conformity according to the present invention, and this content uniformity protocol is incorporated herein by reference. According to this protocol, the content uniformity is determined by measuring the amount of active pharmaceutical ingredient in 10 dosage unit samples, and calculating whether the amount of active pharmaceutical ingredient in all the dosage unit samples falls within a range of 85% to 115% of the target amount. If one dosage unit sample is outside the range of 85% to 115% of the target amount and no unit is outside a range of 75% to 125% of the target amount, or if the Relative Standard Deviation (RSD), which is the sample standard deviation expressed as a percentage of the mean, is not greater than 6%, then 20 additional dosage unit samples are tested. After treating at least 30 dosage units, the content uniformity requirement is met if not more than one dosage unit sample is outside the range of 85% to 115% of the target amount, and no unit is outside a range of 75% to 125% of the target amount, and the RSD of the at least 30 dosage units does not exceed 7.8%.

In certain embodiments, the dissolution profile of the compositions disclosed herein can result in, for example, at least about 50%, at least about 70%, at least about 75%, or at least

about 85%, of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test. In certain embodiments, the dissolution profile of the compositions disclosed herein can comprise at most about 125%, for example at most about 115%, at most about 110%, or at most about 100% of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test. In additional embodiments, the dissolution profile of the compositions disclosed herein can comprise from about 50% to about 125%, for example from about 70% to about 110%, of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

Other embodiments of the present invention are directed to a method of making a pharmaceutical composition comprising:

(a) forming a granule comprising a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein; and

(b) controlling the particle size of the granule such that from about 50% to about 125% of a target amount of calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37° C.±0.5° C., and a rotation speed of 75 r.p.m.

Further embodiments of the present invention are directed to a method of making a pharmaceutical composition comprising:

(b) forming a granule comprising a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein; and

(b) controlling the particle size of the granule such that from about 50% to about 125% of a target amount of calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of about 37° C., and a rotation speed of about 75 r.p.m.

The granule can be formed by any known process, such as high wet shear granulation, low wet shear granulation, fluid bed granulation, rotary granulation, extrusion-spheronization, dry granulation, roller compaction, and the like.

The particle size of the granule of the composition can be controlled by various factors. In certain embodiments of the present invention, the particle size of the granule of the composition can be controlled by the amount of water added to the materials present in a granulator. For example, a desired particle size of the granule can be achieved when the granulator has a volume ranging from about 1 L to about 1200 L, such as from about 65 L to about 1200 L, or from about 300 L to about 800 L, and the amount of water added ranges from about 20% to about 40%, such as from about 30% to about 36%, relative to the amount of dry powders present in the granulator to form the granules.

The granulator's impeller tip speed can also affect the particle size of the granules. In some embodiments, the impeller tip speed, measured in meters per second (m/s), can range from about 5 m/s to about 10 m/s, such as from about 7 m/s to about 9 m/s.

Other embodiments of the present invention are directed to a method of making a pharmaceutical composition comprising

(a) forming a composition comprising a therapeutically effective amount of particles of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein; and

(b) controlling the particle size of the calcium receptor-active compound such that from about 50% to about 125% of a target amount of the calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37° C.±0.5° C., and a rotation speed of 75 r.p.m.

Additional embodiments of the present invention are directed to a method of making a pharmaceutical composition comprising

(a) forming a composition comprising a therapeutically effective amount of particles of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein; and

(b) controlling the particle size of the calcium receptor-active compound such that from about 50% to about 125% of a target amount of the calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of about 37° C., and a rotation speed of about 75 r.p.m.

The size of the particles is controlled during the production of the active pharmaceutical ingredient, for example, by use of a milling step, or a controlled crystallization process. For example, the active pharmaceutical ingredient can be milled using a stainless steel hammer mill with 5 mm screen and 12 hammers forward at a mill speed of 8100±100 rpm, with the feed speed is set at 90±10 rpm.

Yet other embodiments of the present invention are directed to a method for the treatment of a disease or disorder that can be treated by altering a subject's calcium receptor activity. In some embodiments, a method for the treatment of a disease chosen from hyperparathyroidism, such as primary hyperparathyroidism and secondary hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium-phosphorus product comprises administering to a patient, such as human, an effective dosage amount of a pharmaceutical composition comprising a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein, wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37° C.±0.5° C., and at a rotation speed of 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition in no later than about 30 minutes from the start of the test.

A further embodiment of the present invention is directed to a method for the treatment of a disease chosen from hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium-phosphorus product comprises administering to a patient, such as human, an effective dosage amount of a pharmaceutical composition comprising a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein, wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in a USP 2 apparatus at a temperature of about 37° C., and at a rotation speed of about 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition in no later than about 30 minutes from the start of the test.

Reference will now be made to the following examples which are not intended to limit the invention. To the contrary,

it will be appreciated that various alternatives, modifications, and equivalents may be included within the spirit and scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: A process Flow diagram showing a process by which 30-, 60- and 90-mg tablets of active pharmaceutical ingredient are prepared.

EXAMPLES

Three pharmaceutical formulations with target amounts of 30 mg, 60 mg, and 90 mg active pharmaceutical ingredient with the following components were prepared:

	Weight % (w/w)	30 mg Tablet Amount (mg)	60 mg Tablet Amount (mg)	90 mg Tablet Amount (mg)
Cinacalcet HCl	18.367	33.06	66.12	99.18
Pregelatinized starch (Starch 1500)	33.378	60.08	120.16	180.24
Microcrystalline cellulose (Avicel PH102)	6.678	12.02	24.04	36.06
Povidone (Plasdone K29/32)	2.044	3.68	7.36	11.04
Crospovidone (Polyplasdone XL)	1.233	2.22	4.44	6.66
Purified Water[1]	—	—	—	—
Microcrystalline cellulose (Avicel PH102)	34.300	61.74	123.48	185.22
Magnesium stearate	0.500	0.90	1.80	2.70
Colloidal silicon dioxide (Colloidal anhydrous silica) (Cab-O-Sil M5P)	0.500	0.90	1.80	2.70
Crospovidone (Polyplasdone XL)	3.000	5.40	10.80	16.20
Core Tablet	100.000	180.00	360.00	540.00
Purified Water[1]	—	—	—	—
Opadry ® II (colored film former)	4.000	7.20	14.40	21.60
Purified Water[1]	—	—	—	—
Opadry ® Clear (clear film former)	1.500	2.70	5.40	8.10
Carnauba Wax Powder	0.010	0.018	0.036	0.054
Opacode ® Ink (Black)[2] 1	—	—	—	—

[1]The purified Water was removed during processing.
[2]Trace quantities of ink were applied to the coated tablet.

The wet granulation process was conducted in a PMA 800 L high-shear granulator with water serving as the granulation fluid. The cinacalcet HCl and the intra-granulation excipients (pregelatinized starch, microcrystalline cellulose, povidone, and crospovidone) were dry-mixed for 1 to 2 minutes with an impeller speed set point at 116±10 rpm, followed by granulation with 30.0% to 36.0% w/w water (based on intra-granular lot size; target was 34.9% w/w) with an impeller speed set point at 116±10 rpm and at a slow or fast chopper speed (target was slow speed). During the granulation process water was delivered at 9.8±0.5 kg/min.

Following granulation, the mixture was wet-milled using an in-line Comil equipped with a 0.375" (0.953 cm) opening screen and an impeller speed set point at 1400±50 rpm. The mixture was then discharged into a fluid-bed dryer.

After completion of the wet-milling process, the granulation mixture was dried in an Aeromatic MP6 fluid bed dryer with an inlet temperature set point at 70°±5° C. When the outlet temperature reached 37° C. to 41° C., samples were taken to determine moisture levels by loss on drying (LOD). The granules were dried until the average moisture levels reached 1.0% to 2.5%.

The dried granulation mixture was milled through a Quadro Mill 196S (Comil) equipped with a 0.055" (0.140 cm) opening screen at an impeller speed of 1650±50 rpm into a 1000 L Gallay tote.

Except for magnesium stearate, the extra-granular excipients were blended in a 650 L Gallay tote blender for 7±1 minutes at 12±1 rpm. This mixture was further blended with the dry-milled granulation in a 1000 L Gallay tote blender for 15±5 minutes at 12±1 rpm, and then for 6±1 minutes at 12±1 rpm after magnesium stearate was added for lubrication.

The final lubricated blend was compressed into tablets containing 30-, 60-, or 90 mg of the free base equivalent of active cinacalcet HCl using a Unipress 27 tablet press set to a speed of 2000±300 tablets per minute and equipped with a force feeder. Throughout the compression operation, individual tablet weights (target weights of 180, 360, and 540 mg for 30-, 60-, and 90-mg tablets, respectively), the average weight of 10 tablets, tablet hardness and thickness were monitored at pre-determined intervals.

The color-coating suspension and clear-coating solution were prepared by slowly adding either the Opadry® II (green) or Opadry® Clear into purified water while mixing until uniform (≥45 minutes). The color suspension and clear solution deaerated for ≥45 minutes before the spraying process began, and were used within a pre-determined time limit.

Each lot was film-coated with color and clear coats in a Vector Hi-Coater 48" pan. The color-coating suspension was applied onto a moving core tablet bed (pan speed=4 to 7 rpm) and a spray rate of 250±50 grams per minute per 3 guns. The distance between the spray guns and the tablet bed was approximately 8" (20 cm) to 11" (28 cm), and the air volume was 600±200 ft^3 per minute (17.1±5.7 m^3 per minute) with a pan pressure differential maintained between −0.1" (−0.25 cm) to −0.3" (−0.76 cm) of water. Supply air temperature was adjusted to 80±10° C. to maintain an exhaust temperature of 41±3° C.

When the clear-coating application was completed, the heater and the air supply was turned off and the wax was spread evenly over the moving tablet bed (after it reached ≤37° C.) with a pan speed of 4 to 7 rpm. The tablets were rotated for 5±1 minutes, and after the supply air and exhaust fan were turned on, the tablets were rotated for an additional 5±1 minutes with a pan speed of 4 to 7 rpm and supply air of 600±200 ft^3 per minute (17.1±5.7 m^3 per minute). The pan was jogged until the tablet bed temperature reached ≤30° C.

An Ackley ink-based offset printer was used to produce 2-sided printed tablets.

The dissolution profile of the three formulations were measured according the dissolution protocol described in the USP 26/NF 21, chapter 711 using a USP 2 apparatus at a temperature of about 37° C., and at a rotation speed of about 75 r.p.m. The dissolution profile of the formulations in which at least about 75% of the cinacalcet HCl was released from the composition in no later than about 30 minutes from the start of the test is set forth in Table 2.

TABLE 2

Time (min)	30 mg Tablet	60 mg Tablet	90 mg Tablet
15	85.3	81.9	80.8
30	95.2	93.8	93.4
45	97.7	97.7	97.9
60	98.7	98.8	99.8

The content uniformity of the three formulations were measured in accordance with USP 26/NF 21, chapter 905,

described in detail above. The content uniformity and for each of the three formulations is set forth in Table 3.

TABLE 3

	30 mg Tablet		60 mg Tablet		90 mg Tablet	
Container	Mean (10 tablets)	% RSD	Mean (10 tablets)	% RSD	Mean (10 tablets)	% RSD
1 (beg.)	98.5	0.8	96.7	1.6	99.7	1.2
5	98.8	0.8	98.5	0.8	100.7	0.9
11	98.5	0.6	98.3	1.0	99.9	0.7
16	98.3	0.8	97.6	1.3	99.9	0.5
22	98.3	1.0	96.3	1.8	100.7	0.9
end	98.0	0.6	95.8	1.9	99.3	0.8

What is claimed is:

1. A pharmaceutical composition comprising:
(a) from about 10% to about 40% by weight of cinacalcet HCl in an amount of from about 20 mg to about 100 mg;
(b) from about 45% to about 85% by weight of a diluent selected from the group consisting of microcrystalline cellulose, starch, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins, and mixtures thereof,
(c) from about 1% to about 5% by weight of at least one binder selected from the group consisting of povidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, and mixtures thereof; and
(d) from about 1% to 10% by weight of at least one disintegrant selected from the group consisting of crospovidine, sodium starch glycolate, croscarmellose sodium, and mixtures thereof,
wherein the percentage by weight is relative to the total weight of the composition, and wherein the composition is for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

2. The composition according to claim 1, further comprising at least one excipient selected from the group consisting of lubricants and clear and color coating materials.

3. The composition according to claim 1, further comprising from about 1% to about 6% by weight of at least one coating material selected from the group consisting of clear and color coating materials wherein the percentage by weight is relative to the total weight of the composition.

4. The composition according to claim 1, further comprising from about 0.05% to about 5% of at least one additive selected from the group consisting of glidants, lubricants and adherents, wherein the percentage by weight is relative to the total weight of the composition.

5. The composition according to claim 1, wherein the at least one binder is povidone.

6. The composition according to claim 1, wherein the at least one disintegrant is crospovidone.

7. The composition according to claim 6 wherein the form of the cinacalcet HCl is selected from the group consisting of needle-shape particles, rod-shape particles, plate-shaped particles, and mixtures thereof.

8. The composition according to claim 1, wherein the cinacalcet HCl is in a form selected from the group consisting of amorphous powders, crystalline particles, and mixtures thereof.

9. The composition according to claim 8 wherein the particle D_{50} of the cinacalcet HCl particles is less than or equal to about 50 μm.

10. The composition according to claim 9, wherein the granules have a granule D_{50} measured using a sieve analysis ranging from about 50 μm to about 150 μm.

11. The composition according to claim 9, wherein the granules have a granule D_{50} measured using a sieve analysis ranging from about 80 μm to about 130 μm.

12. The composition according to claim 11, wherein the crospovidone is present intergranularly.

13. The composition according to claim 11, wherein the crospovidone is present intragranularly.

14. The composition according to claim 9, wherein the disintegrant is crospovidone and the crospovidone is present intergranularly, intragranularly, or a combination thereof.

15. The composition according to claim 1 wherein the composition comprises granules.

16. The composition according to claim 1 further comprising from about 0.05% to about 1.5% by weight of colloidal silicon dioxide relative to the total weight of the composition.

17. The composition according to claim 1 further comprising from about 0.05% to about 1.5% by weight of magnesium stearate relative to the total weight of the composition.

18. The composition according to claim 1, wherein the hyperparathyroidism is primary hyperparathyroidism or secondary hyperparathyroidism.

19. The composition according to claim 1, wherein the diluent is microcrystalline cellulose or starch.

20. A pharmaceutical composition comprising:
(a) from about 10% to about 40% by weight of cinacalcet HCl in an amount of from about 20 mg to about 100 mg;
(b) from about 45% to about 85% by weight of a diluent selected from the group consisting of microcrystalline cellulose, starch, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins, and mixtures thereof,
(c) from about 1% to about 5% by weight of at least one binder selected from the group consisting of povidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, and mixtures thereof; and
(d) from about 1% to 10% by weight of at least one disintegrant selected from the group consisting of crospovidine, sodium starch glycolate, croscarmellose sodium, and mixtures thereof,
wherein the disintegrant is at least present intragranularly and wherein the composition is for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

21. A pharmaceutical composition comprising:
(a) from about 10% to about 40% by weight of cinacalcet HCl in an amount of from about 20 mg to about 100 mg;
(b) from about 5% to about 10% by weight of starch;
(b) from about 40% to about 75% by weight of microcrystalline cellulose,
(c) from about 1% to about 5% by weight of povidone, and
(d) from about 1% to 10% by weight of crospovidone,
wherein the percentage by weight is relative to the total weight of the composition, and wherein the composition is for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

22. The composition according to claim 21 further comprising from about 0.05% to about 1.5% by weight of colloidal silicon dioxide relative to the total weight of the composition.

23. The composition according to claim 21 further comprising from about 0.05% to about 1.5% by weight of magnesium stearate relative to the total weight of the composition.

* * * * *

EXHIBIT 2

Pharmaceutics

The Science of Dosage Form Design

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To improve the flow properties of the mix

Many powders, because of their small size, irregular shape or surface characteristics, are cohesive and do not flow well. Poor flow will often result in a wide weight variation within the final product owing to variable fill of tablet dies etc. Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties.

To improve the compaction characteristics of the mix

Some powders are difficult to compact even if a readily compactable adhesive is included in the mix, but granules of the same formulation are often more easily compacted and produce stronger tablets. This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granule. Often solute migration (see Chapter 26) occurring during the postgranulation drying stage results in a binder-rich outer layer to the granules. This in turn leads to direct binder–binder bonding, which assists the consolidation of weakly bonding materials.

Other reasons

The above are the primary reasons for the granulation of pharmaceutical products, but there are other reasons that may necessitate the granulation of powdered material:

1. The granulation of toxic materials will reduce the hazard associated with the generation of toxic dust that may arise when handling powders. Suitable precautions must be taken to ensure that such dust is not a hazard during the granulation process. Thus granules should be non-friable and have a suitable mechanical strength.
2. Materials which are slightly hygroscopic may adhere and form a cake if stored as a powder. Granulation may reduce this hazard, as the granules will be able to absorb some moisture and yet retain their flowability because of their size.
3. Granules, being denser than the parent powder mix, occupy less volume per unit weight. They are therefore more convenient for storage or shipment.

Methods of granulation

Granulation methods can be divided into two types: **wet** methods, which use a liquid in the process, and ***dry*** methods in which no liquid is used.

In a suitable formulation a number of different excipients will be needed in addition to the drug. The common types used are diluents, to produce a unit dose weight of suitable size, and disintegrating agents, which are added to aid the break-up of the granule when it reaches a liquid medium, e.g. on ingestion by the patient. Adhesives in the form of a dry powder may also be added, particularly if dry granulation is employed. These ingredients will be mixed before granulation.

Dry granulation

In the dry methods of granulation the primary powder particles are aggregated under high pressure. There are two main processes. Either a large tablet (known as a '***slug***') is produced in a heavy-duty tabletting press (a process known as '***slugging***') or the powder is squeezed between two rollers to produce a sheet of material ('***roller compaction***'). In both cases these intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to separate the desired size fraction. The unused fine material may be reworked to avoid waste. This dry method may be used for drugs that do not compress well after wet granulation, or those which are sensitive to moisture.

Wet granulation (involving wet massing)

Wet granulation involves the massing of a mix of dry ***primary powder particles*** using a ***granulating fluid***. The fluid contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic. Typical liquids include water, ethanol and isopropanol, either alone or in combination. The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved ***adhesive*** (also referred to as a ***binder*** or ***binding agent***) which is used to ensure particle adhesion once the granule is dry.

Water is commonly used for economical and ecological reasons. Its disadvantages as a solvent are that it may adversely affect drug stability, causing hydrolysis of susceptible products, and it needs a longer drying time than do organic solvents. This increases the length of the process and again may affect stability because of the extended exposure to heat. The primary advantage of water is that it is non-flammable, which means that expensive safety precautions such as the use of flameproof equipment need not be taken. Organic solvents are used when

water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required.

In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which are then dried. A subsequent screening stage breaks agglomerates of granules and removes the fine material, which can than be recycled. Variations of this traditional method depend on the equipment used, but the general principle of initial particle aggregation using a liquid remains in all of the processes.

Effect of granulation method on granule structure

The type and capacity of granulating mixers significantly influences the work input and time necessary to produce a cohesive mass, adequate liquid distribution and intragranular porosity of the granular mass. The method and conditions of granulation affect intergranular and intragranular pore structure by changing the degree of packing within the granules. It has been shown that precompressed granules, consisting of compressed drug and binder particles, are held together by simple bonding during compaction. Granules prepared by wet massing consist of intact drug particles held together in a sponge-like matrix of binder. Fluidized-bed granules are similar to those prepared by the wet massing process, but possess greater porosity and the granule surface is covered by a film of binding agent. With spray-dried systems the granules consist of spherical particles composed of an outer shell and an inner core of particles. Thus the properties of the granule are influenced by the manufacturing process.

GRANULATION MECHANISMS

Particle-bonding mechanisms

To form granules, bonds must be formed between powder particles so that they adhere and these bonds must be sufficiently strong to prevent breakdown of the granule to powder in subsequent handling operations.

There are five primary bonding mechanisms between particles:

1. Adhesion and cohesion forces in the immobile liquid films between individual primary powder particles;
2. Interfacial forces in mobile liquid films within the granules;
3. The formation of solid bridges after solvent evaporation;
4. Attractive forces between solid particles;
5. Mechanical interlocking.

Different types of mechanism were identified in each group and the ones discussed below are those that are relevant to pharmaceutical granulations.

Adhesion and cohesion forces in immobile films

If sufficient liquid is present in a powder to form a very thin, immobile layer, there will be an effective decrease in interparticulate distance and an increase in contact area between the particles. The bond strength between the particles will be increased because of this, as the van der Waals forces of attraction are proportional to the particle diameter and inversely proportional to the square of the distance of separation.

This situation will arise with adsorbed moisture and accounts for the cohesion of slightly damp powders. Although such films may be present as residual liquid after granules prepared by wet granulation have been dried, it is unlikely that they contribute significantly to the final granule strength. In dry granulation, however, the pressures used will increase the contact area between the adsorption layers and decrease the interparticulate distance, and this will contribute to the final granule strength.

Thin, immobile layers may also be formed by highly viscous solutions of adhesives, and so the bond strength will be greater than that produced by the mobile films discussed below. The use of starch mucilage in pharmaceutical granulations may produce this type of film.

Interfacial forces in mobile liquid films

During wet granulation liquid is added to the powder mix and will be distributed as films around and between the particles. Sufficient liquid is usually added to exceed that necessary for an immobile layer and to produce a mobile film. There are three states of water distribution between particles, which are illustrated in Figure 25.2.

At low moisture levels, termed the ***pendular state***, the particles are held together by lens-shaped rings of liquid. These cause adhesion because of the surface tension forces of the liquid/air interface and the hydrostatic suction pressure in the liquid bridge. When all the air has been displaced from between

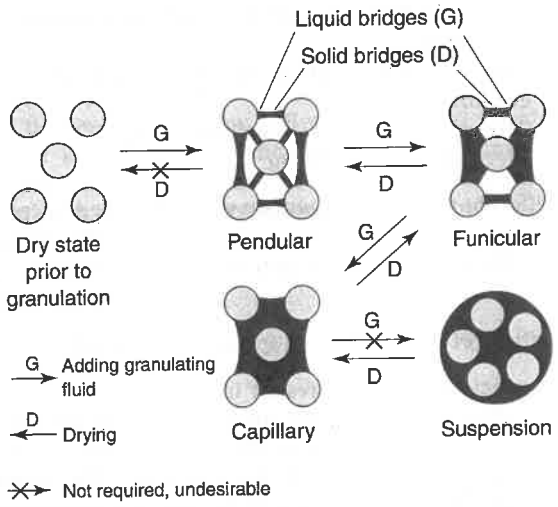


Fig. 25.2 Water distribution between particles of a granule during formation and drying.

the particles the ***capillary state*** is reached, and the particles are held by capillary suction at the liquid/air interface, which is now only at the granule surface. The ***funicular state*** represents an intermediate stage between the pendular and capillary states. Moist granule tensile strength increases about three times between the pendular and the capillary state.

It may appear that the state of the powder bed is dependent upon the total moisture content of the wetted powders, but the capillary state may also be reached by decreasing the separation of the particles. In the massing process during wet granulation, continued kneading/mixing of material originally in the pendular state will densify the wet mass, decreasing the pore volume occupied by air and eventually producing the funicular or capillary state without further liquid addition.

In addition to these three states, a further state, the droplet, is illustrated in Figure 25.2. This will be important in the process of granulation by spray-drying of a suspension. In this state, the strength of the droplet is dependent upon the surface tension of the liquid used.

These wet bridges are only temporary structures in wet granulation because the moist granules will be dried. They are, however, a prerequisite for the formation of solid bridges formed by adhesives present in the liquid, or by materials that dissolve in the granulating liquid.

Solid bridges

These can be formed by:

1. partial melting
2. hardening binders
3. crystallization of dissolved substances.

Partial melting Although not considered to be a predominant mechanism in pharmaceutical materials, it is possible that the pressures used in dry granulation methods may cause melting of low melting-point materials where the particles touch and high pressures are developed. When the pressure is relieved, crystallization will take place and bind the particles together.

Hardening binders This is the common mechanism in pharmaceutical wet granulations when an adhesive is included in the granulating solvent. The liquid will form liquid bridges, as discussed above, and the adhesive will harden or crystallize on drying to form solid bridges to bind the particles. Adhesives such as polyvinylpyrrolidone, the cellulose derivatives (such as carboxymethylcellulose) and pregelatinized starch function in this way.

Crystallization of dissolved substances The solvent used to mass the powder during wet granulation may partially dissolve one of the powdered ingredients. When the granules are dried, crystallization of this material will take place and the dissolved substance then acts as a hardening binder. Any material soluble in the granulating liquid will function in this manner, e.g. lactose incorporated into dry powders granulated with water.

The size of the crystals produced in the bridge will be influenced by the rate of drying of the granules: the slower the drying time, the larger the particle size. It is therefore important that the drug does not dissolve in the granulating liquid and recrystallize, because it may adversely affect the dissolution rate of the drug if crystals larger than that of the starting material are produced.

Attractive forces between solid particles

In the absence of liquids and solid bridges formed by binding agents, there are two types of attractive force that can operate between particles in pharmaceutical systems.

Electrostatic forces may be important in causing powder cohesion and the initial formation of agglomerates, e.g. during mixing. In general they do not contribute significantly to the final strength of the granule.

Van der Waals forces, however, are about four orders of magnitude greater than electrostatic forces and contribute significantly to the strength of granules produced by dry granulation. The magnitude of these forces will increase as the distance between

procedure. The degree of crystallinity will affect the physical and technical properties of the particles, e.g. in terms of hygroscopicity and powder compactability.

Microcrystalline cellulose is prepared by hydrolysis of cellulose followed by spray drying. The particles thus formed are aggregates of smaller cellulose fibres. Depending on the preparation conditions, aggregates of different particle size can be prepared which have different flowabilities.

A final important example of a common filler is an inorganic substance, dicalcium phosphate dihydrate. This is insoluble in water and non-hygroscopic but is hydrophilic, i.e. easily wetted by water. The substance can be obtained both in a fine particulate form, mainly used in granulation, and in an aggregated form. The latter possesses good flowability and is used in tablet production by direct compaction. Calcium phosphate is slightly alkaline and may thus be incompatible with drugs sensitive to alkaline conditions.

Disintegrant

A disintegrant is included in the formulation to ensure that the tablet, when in contact with a liquid, breaks up into small fragments, which promotes rapid drug dissolution. Ideally, the tablet should break up into individual drug particles in order to obtain the largest possible effective surface area during dissolution.

The disintegration process for a tablet occurs in two steps. First, the liquid wets the solid and penetrates the pores of the tablet. Thereafter, the tablet breaks into smaller fragments. The actual fragmentation of the tablet can also occur in steps, i.e. the tablet disintegrates into aggregates of primary particles which subsequently deaggregate into their primary drug particles. A deaggregation directly into primary powder particles will set up conditions for the fastest possible dissolution of the drug. A scheme for the release of the drug from a disintegrating tablet is shown in Fig. 27.7.

Several mechanisms of action of disintegrants have been suggested, such as swelling of particles, exothermic wetting reaction, particle repulsion and particle deformation recovery. However, as two main processes are involved in the disintegration event, disintegrants to be used in plain tablets are here classified into two types:

1. *Disintegrants that facilitate water uptake.* These disintegrants act by facilitating the transport of liquids into the pores of the tablet, with the consequence that the tablet may break into fragments. One obvious type of substance that can promote liquid penetration are surface activ agents. Such substances are used to make the drug particle surfaces more hydrophilic and thu promote the wetting of the solid and the penetration of the liquid into the pores of the tablet. It has also been suggested that other substances can promote the liquid penetration using capillary forces to suck water into the pores of the tablet.
2. *Disintegrants that will rupture the tablet.* Rupturin of tablets can be caused by swelling of the disintegrant particles during sorption of water. However, it has also been suggested that non-swelling disintegrants can break the tablet, and different mechanisms have been suggested. One such concerns a repulsion of particles in contac with water and another the recovery of deforme particles to their original shape in contact with water, i.e. particles which have been deformed during compaction.

The most traditionally used disintegrant in conve tional tablets is starch, among which potato, mai and corn starches are the most common types use The typical concentration range of starch in a tabl formulation is up to 10%. Starch particles swell contact with water and this swelling can subs quently disrupt the tablet. However, it has al been suggested that starch particles may facilita disintegration by particle–particle repulsion.

The most common and effective disintegrants a via a swelling mechanism and a series of effecti swelling disintegrants have been developed whi can swell dramatically during water uptake and th quickly and effectively break the tablet. These a normally modified starch or modified cellulos High-swelling disintegrants are included in the fo mulation at relatively low concentrations, typical 1–5% by weight.

Disintegrants can be mixed with other ingredien prior to granulation and thus be incorporated with the granules (intragranular addition). It is al common for the disintegrant to be mixed with t dry granules before the complete powder mix compacted (extragranular addition). The latter pr cedure will contribute to an effective disintegrati of the tablet into smaller fragments. Disintegran may also be incorporated as both an intragranul and an extragranular portion.

A third group of disintegrants functions by produ ing gas, normally carbon dioxide, in contact wi water. Such disintegrants are used in effervesce tablets and normally not in tablets that should be swa lowed as a solid. The liberation of carbon dioxide

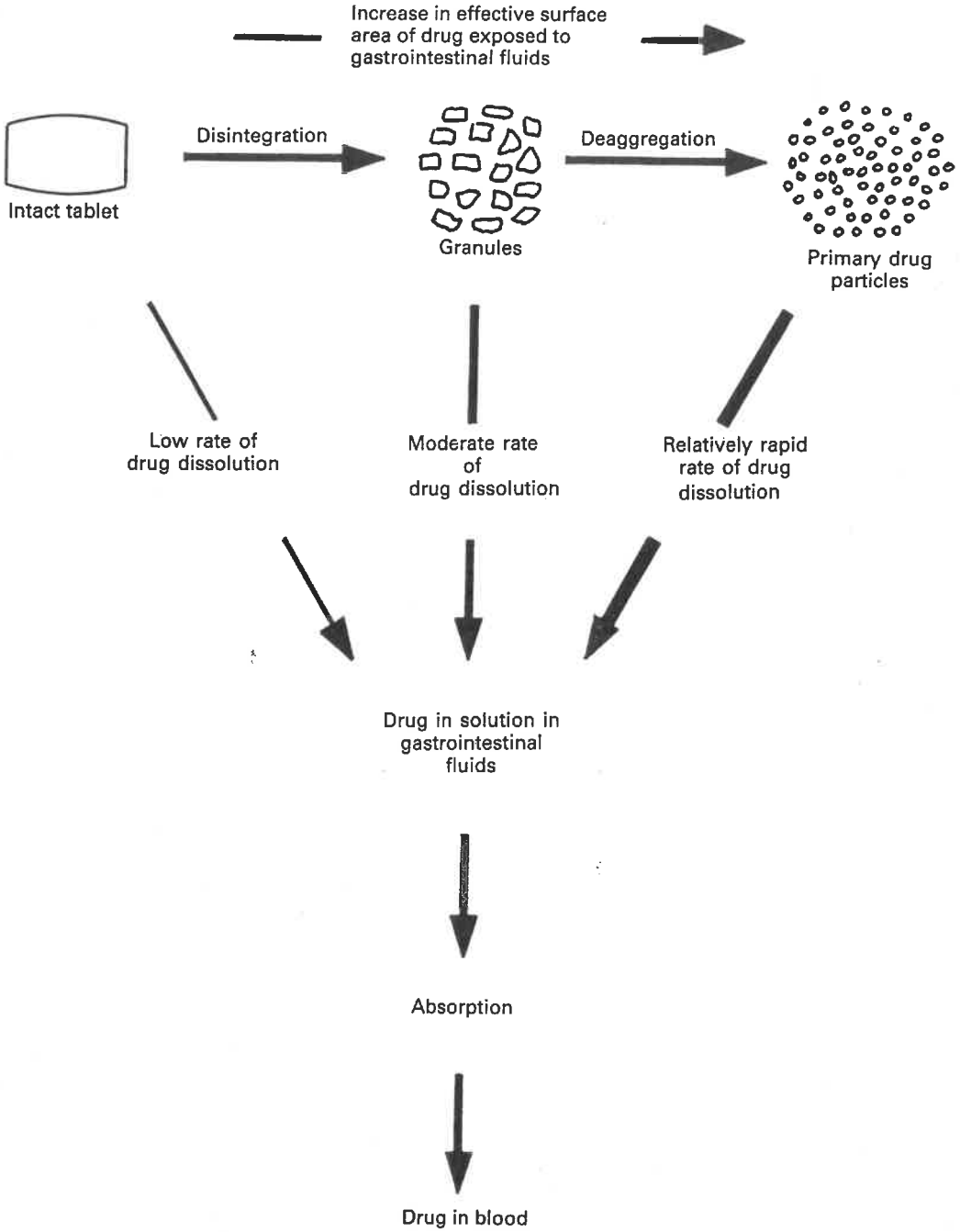


Fig. 27.7 Mechanistic representation of the drug release process from a tablet by disintegration and dissolution. From Wells, J.I. and Rubinstein, M.W. (1976) *Pharm. J.* **217**, 629.

obtained by the decomposition of bicarbonate or carbonate salts in contact with acidic water. The acidic pH is accomplished by the incorporation of a weak acid in the formulation, such as citric acid and tartaric acid.

Binder

A binder (also sometimes called adhesive) is added to a drug–filler mixture to ensure that granules and tablets can be formed with the required mechanical

strength. Binders can be added to a powder in different ways:

- As a dry powder which is mixed with the other ingredients before wet agglomeration. During the agglomeration procedure the binder might thus dissolve partly or completely in the agglomeration liquid;
- As a solution which is used as agglomeration liquid during wet agglomeration. The binder is here often referred to as a ***solution binder***.
- As a dry powder which is mixed with the other ingredients before compaction (slugging or tabletting). The binder is here often referred to as a ***dry binder***.

Both solution binders and dry binders are included in the formulation at relatively low concentrations, typically 2–10% by weight. Common traditional solution binders are starch, sucrose and gelatin. More commonly used binders today, with improved adhesive properties, are polymers such as polyvinylpyrrolidone and cellulose derivatives (in particular hydroxypropyl methylcellulose). Important examples of dry binders are microcrystalline cellulose and crosslinked polyvinylpyrrolidone.

Solution binders are generally considered the most effective, and this is therefore the most common way of incorporating a binder into granules; the granules thus formed are often referred to as binder–substrate granules. It is not uncommon, however, for a dry binder to be added to the dry binder–substrate granules before tabletting in order to further improve the compactability of the granulation.

Glidant

The role of the glidant is to improve the flowability of the powder. This is especially important during tablet production at high production speeds and during direct compaction. However, because the requirement for adequate flow is high, a glidant is often also added to a granulation before tabletting.

Traditionally, talc has been used as a glidant in tablet formulations, in concentrations of about 1–2% by weight. Today, the most commonly used glidant is probably colloidal silica, added in very low proportions (about 0.2% by weight). Because the silica particles are very small they adhere to the particle surfaces of the other ingredients and improve flow by reducing interparticulate friction. Magnesium stearate, normally used as a lubricant, can also promote powder flow at low concentrations (< 1% by weight).

Lubricant

The function of the lubricant is to ensure that tablet formation and ejection can occur with low friction between the solid and the die wall. High friction during tabletting can cause a series of problems, including inadequate tablet quality (capping or even fragmentation of tablets during ejection, and vertical scratches on tablet edges) and may even stop production. Lubricants are thus included in almost all tablet formulations.

Lubrication is achieved by mainly two mechanisms: ***fluid lubrication*** and ***boundary lubrication*** (Fig. 27.8). In fluid lubrication a layer of fluid is located between and separates the moving surfaces of the solids from each other and thus reduces the friction. Fluid lubricants are seldom used in tablet formulations. However, liquid paraffin has been used, such as in formulations for effervescent tablets.

Boundary lubrication is considered as a surface phenomenon, as here the sliding surfaces are separated by only a very thin film of lubricant. The nature of the solid surfaces will therefore affect friction. In boundary lubrication the friction coefficient and wear of the solids are higher than with fluid lubrication. All substances that can affect interaction between sliding surfaces can be described as boundary lubricants, including adsorbed gases. The lubricants used in tablet formulations acting by boundary lubrication are fine particulate solids.

A number of mechanisms have been discussed for these boundary lubricants, including that lubricants are substances that show a low resistance towards shearing. The most effective of the boundary lubricants are stearic acid or stearic acid salts, primarily

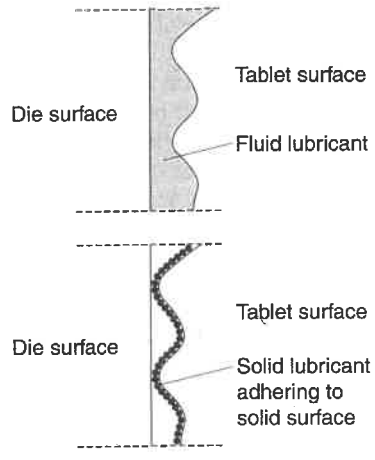


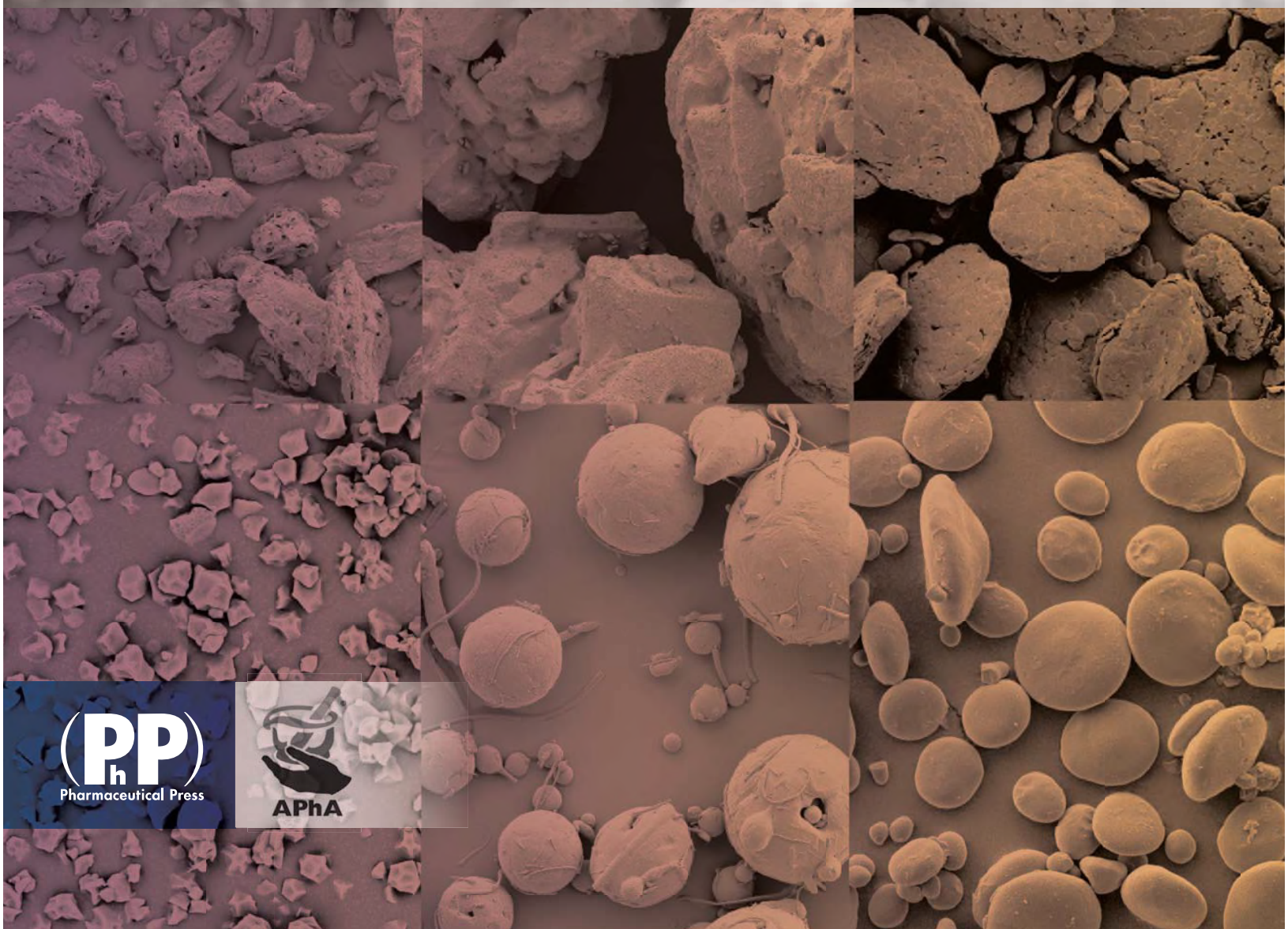
Fig. 27.8 Schematic illustration of lubrication mechanisms by fluid and boundary lubrication.

EXHIBIT 3

Handbook of Pharmaceutical Excipients

Sixth edition

Edited by
Raymond C Rowe, Paul J Sheskey and Marian E Quinn



Pharmaceutical Press
APhA

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material. However, as with other cellulose derivatives, oral consumption of large amounts of carboxymethylcellulose calcium may have a laxative effect.

See also Carboxymethylcellulose Sodium.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Carboxymethylcellulose calcium may be irritant to the eyes; eye protection is recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (oral, capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Carboxymethylcellulose sodium; croscarmellose sodium.

18 Comments

Carboxymethylcellulose calcium is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

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21 Author

JC Hooton.

22 Date of Revision

3 February 2009.

Carboxymethylcellulose Sodium

1 Nonproprietary Names

BP: Carmellose Sodium

JP: Carmellose Sodium

PhEur: Carmellose Sodium

USP: Carboxymethylcellulose Sodium

2 Synonyms

Akucell; *Aqualon CMC*; *Aquasorb*; *Blanose*; *Carbose D*; carmellosum natricum; *Cel-O-Brandt*; cellulose gum; *Cethylose*; CMC sodium; E466; *Finnfix*; *Glykocellan*; *Nymcel ZSB*; SCMC; sodium carboxymethylcellulose; sodium cellulose glycolate; *Sunrose*; *Tylose CB*; *Tylose MGA*; *Walocel C*; *Xylo-Mucine*.

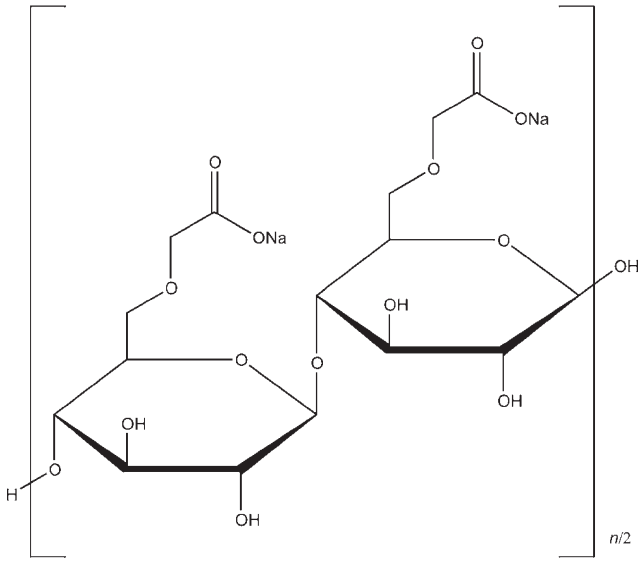
3 Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]

4 Empirical Formula and Molecular Weight

The USP 32 describes carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose.

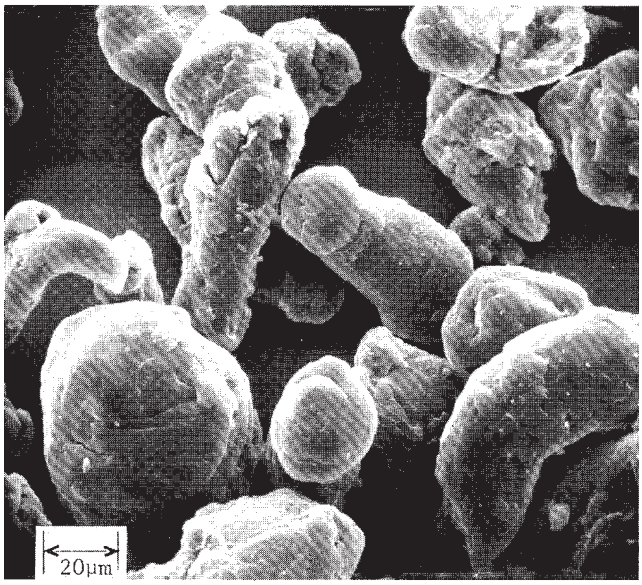
5 Structural Formula



Structure shown with a degree of substitution (DS) of 1.0.

SEM 1: Excipient: carboxymethylcellulose sodium; manufacturer: Buckeye Cellulose Corp.; lot no.: 9247 AP; magnification: 120×; voltage: 10 kV.

SEM 2: Excipient: carboxymethylcellulose sodium; manufacturer: Ashland Aqualon Functional Ingredients; lot no.: 21 A-1 (44390); magnification: 600×; voltage: 10 kV.



6 Functional Category

Coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent; water-absorbing agent.

7 Applications in Pharmaceutical Formulation or Technology

Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration.[1,2] Carboxymethylcellulose sodium may also be used as a tablet binder and disintegrant,[3–6] and to stabilize emulsions.[7,8]

Higher concentrations, usually 3–6%, of the medium-viscosity grade are used to produce gels that can be used as the base for applications and pastes; glycols are often included in such gels to prevent them drying out. Carboxymethylcellulose sodium is also used in self-adhesive ostomy, wound care,[9] and dermatological patches as a muco-adhesive and to absorb wound exudate or transepidermal water and sweat. This muco-adhesive property is used in products designed to prevent post-surgical tissue adhesions;[10-12] and to localize and modify the release kinetics of active ingredients applied to mucous membranes; and for bone repair. Encapsulation with carboxymethylcellulose sodium can affect drug protection and delivery.[6,13] There have also been reports of its use as a cyto-protective agent.[14,15]

Carboxymethylcellulose sodium is also used in cosmetics, toiletries,[16] surgical prosthetics,[17] and incontinence, personal hygiene, and food products.

See Table I.

Table I: Uses of carboxymethylcellulose sodium.

Use	Concentration (%)
Emulsifying agent	0.25–1.0
Gel-forming agent	3.0–6.0
Injections	0.05–0.75
Oral solutions	0.1–1.0
Tablet binder	1.0–6.0

8 Description

Carboxymethylcellulose sodium occurs as a white to almost white, odorless, tasteless, granular powder. It is hygroscopic after drying. *See also* Section 18.

9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

Table II: Pharmacopeial specifications for carboxymethylcellulose sodium.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	+	+	—
pH (1% w/v solution)	6.0–8.0	6.0–8.0	6.5–8.5
Appearance of solution	+	+	—
Viscosity	—	+	+
Loss on drying	⩽10.0%	⩽10.0%	⩽10.0%
Heavy metals	⩽20 ppm	⩽20 ppm	⩽0.002%
Chloride	⩽0.640%	⩽0.25%	—
Arsenic	⩽10 ppm	—	—
Sulfate	⩽0.960%	—	—
Silicate	⩽0.5%	—	—
Sodium glycolate	—	⩽0.4%	—
Starch	+	—	—
Sulfated ash	—	20.0–33.3%	—
Assay (of sodium)	6.5–8.5%	6.5–10.8%	6.5–9.5%

10 Typical Properties

Density (bulk) 0.52 g/cm^3
Density (tapped) 0.78 g/cm^3
Dissociation constant pK_a = 4.30
Melting point Browns at approximately 227°C, and chars at approximately 252°C.
Moisture content Typically contains less than 10% water. However, carboxymethylcellulose sodium is hygroscopic and absorbs significant amounts of water at temperatures up to 37°C at relative humidities of about 80%. *See* Section 11. *See also* Figure 1.
NIR spectra *see* Figure 2.
Solubility Practically insoluble in acetone, ethanol (95%), ether, and toluene. Easily dispersed in water at all temperatures,

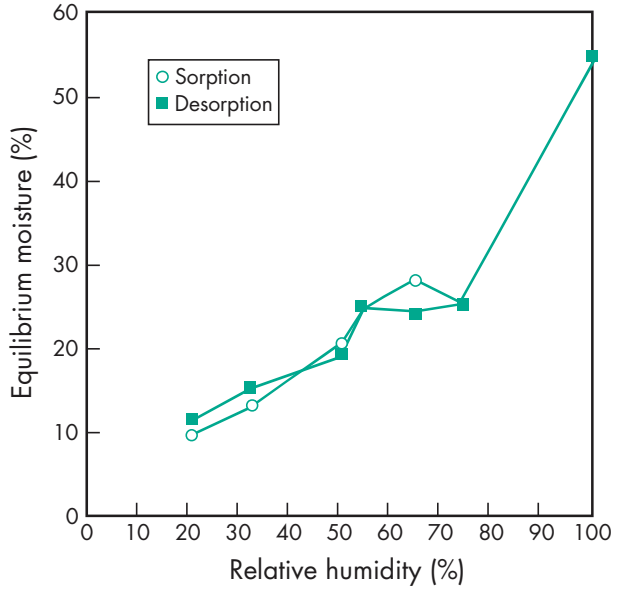


Figure 1: Sorption–desorption isotherm of carboxymethylcellulose sodium.

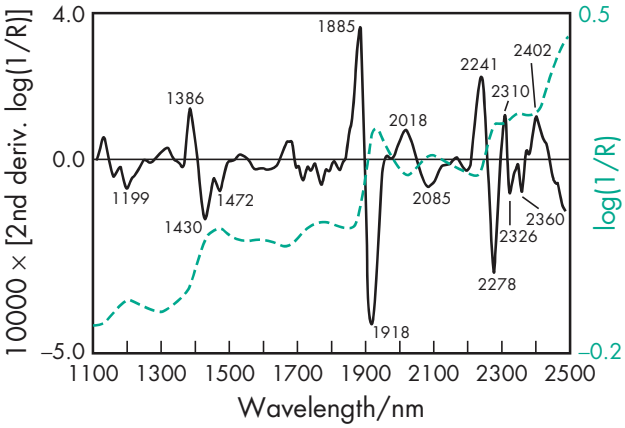


Figure 2: Near-infrared spectrum of carboxymethylcellulose sodium measured by reflectance.

Table III: Viscosity of aqueous carboxymethylcellulose sodium 1% w/v solutions. (Measurements made with a Brookfield LVT viscometer at 25°C.)

	Grade	Viscosity (mPa s)	Spindle	Speed
Low viscosity	*Akucell AF 0305*	10–15	#1	60 rpm
Medium viscosity	*Akucell AF 2785*	1500–2500	#3	30 rpm
High viscosity	*Akucell AF 3085*	8000–12000	#4	30 rpm

forming clear, colloidal solutions. The aqueous solubility varies with the degree of substitution (DS). *See* Section 18.

Viscosity Various grades of carboxymethylcellulose sodium are commercially available that have differing aqueous viscosities; *see* Table III. Aqueous 1% w/v solutions with viscosities of 5–2000 mPa s (5–2000 cP) may be obtained. An increase in concentration results in an increase in aqueous solution viscosity.[16] Prolonged heating at high temperatures will depolymerize the gum and permanently decrease the viscosity. The viscosity of sodium carboxymethylcellulose solutions is fairly stable over a pH range of 4–10. The optimum pH range is neutral. *See* Section 11.

11 Stability and Storage Conditions

Carboxymethylcellulose sodium is a stable, though hygroscopic material. Under high-humidity conditions, carboxymethylcellulose sodium can absorb a large quantity (>50%) of water. In tablets, this has been associated with a decrease in tablet hardness and an increase in disintegration time.[18]

Aqueous solutions are stable at pH 2–10; precipitation can occur below pH 2, and solution viscosity decreases rapidly above pH 10. Generally, solutions exhibit maximum viscosity and stability at pH 7–9.

Carboxymethylcellulose sodium may be sterilized in the dry state by maintaining it at a temperature of 160°C for 1 hour. However, this process results in a significant decrease in viscosity and some deterioration in the properties of solutions prepared from the sterilized material.

Aqueous solutions may similarly be sterilized by heating, although this also results in some reduction in viscosity. After autoclaving, viscosity is reduced by about 25%, but this reduction is less marked than for solutions prepared from material sterilized in the dry state. The extent of the reduction is dependent on the molecular weight and degree of substitution; higher molecular weight grades generally undergo a greater percentage reduction in viscosity.[19] Sterilization of solutions by gamma irradiation also results in a reduction in viscosity.

Aqueous solutions stored for prolonged periods should contain an antimicrobial preservative.[20]

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Carboxymethylcellulose sodium is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. It is also incompatible with xanthan gum. Precipitation may occur at pH < 2, and also when it is mixed with ethanol (95%).

Carboxymethylcellulose sodium forms complex coacervates with gelatin and pectin. It also forms a complex with collagen and is capable of precipitating certain positively charged proteins.

13 Method of Manufacture

Alkali cellulose is prepared by steeping cellulose obtained from wood pulp or cotton fibers in sodium hydroxide solution. The alkaline cellulose is then reacted with sodium monochloroacetate to produce carboxymethylcellulose sodium. Sodium chloride and sodium glycolate are obtained as by-products of this etherification.

14 Safety

Carboxymethylcellulose sodium is used in oral, topical, and some parenteral formulations. It is also widely used in cosmetics, toiletries, and food products, and is generally regarded as a nontoxic and nonirritant material. However, oral consumption of large amounts of carboxymethylcellulose sodium can have a laxative effect; therapeutically, 4–10 g in daily divided doses of the medium- and high-viscosity grades of carboxymethylcellulose sodium have been used as bulk laxatives.[21]

The WHO has not specified an acceptable daily intake for carboxymethylcellulose sodium as a food additive since the levels necessary to achieve a desired effect were not considered to be a hazard to health.[22–25] However, in animal studies, subcutaneous administration of carboxymethylcellulose sodium has been found to cause inflammation, and in some cases of repeated injection fibrosarcomas have been found at the site of injection.[26]

Hypersensitivity and anaphylactic reactions have occurred in cattle and horses, which have been attributed to carboxymethylcellulose sodium in parenteral formulations such as vaccines and penicillins.[27–30]

LD_{50} (guinea pig, oral): 16 g/kg[31]

LD_{50} (rat, oral): 27 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Carboxymethylcellulose sodium may be irritant to the eyes. Eye protection is recommended.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Database (dental preparations; intra-articular, intrabursal, intradermal, intralesional, and intrasynovial injections; oral drops, solutions, suspensions, syrups and tablets; topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Carboxymethylcellulose calcium.

18 Comments

Carboxymethylcellulose sodium is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

A number of grades of carboxymethylcellulose sodium are commercially available, such as *Accelerate*. These have a degree of substitution (DS) in the range 0.7–1.2. The DS is defined as the average number of hydroxyl groups substituted per anhydroglucose unit and it is this that determines the aqueous solubility of the polymer. Thermal crosslinking reduces solubility while retaining water absorption, therefore producing materials suitable for water absorption.

Grades are typically classified as being of low, medium, or high viscosity. The degree of substitution and the maximum viscosity of an aqueous solution of stated concentration should be indicated on any carboxymethylcellulose sodium labeling.

Carboxymethylcellulose sodium has been reported to give false positive results in the LAL test for endotoxins.[32]

The PubChem Compound ID (CID) for carboxymethylcellulose sodium is 23706213.

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21 Author

JC Hooton.

22 Date of Revision

3 February 2009.

14 Safety

Hydrogenated castor oil is used in oral and topical pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material.

Acute oral toxicity studies in animals have shown that hydrogenated castor oil is a relatively nontoxic material. Irritation tests with rabbits show that hydrogenated castor oil causes mild, transient irritation to the eye.

LD_{50} (rat, oral): >10 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Accepted in the USA as an indirect food additive. Included in the FDA Inactive Ingredients Database (oral capsules, tablets, and sublingual tablets).

Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Castor oil; vegetable oil, hydrogenated.

18 Comments

Various different grades of hydrogenated castor oil are commercially available, the composition of which may vary considerably. *Sterotex K* (Karlshamns Lipid Specialities), for example, is a mixture of hydrogenated castor oil and hydrogenated cottonseed oil. *See* Vegetable Oil, hydrogenated for further information.

The EINECS number for hydrogenated castor oil is 232-292-2.

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20 General References

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21 Author

RT Guest.

22 Date of Revision

11 February 2009.

Cellulose, Microcrystalline

1 Nonproprietary Names

BP: Microcrystalline Cellulose
JP: Microcrystalline Cellulose
PhEur: Cellulose, Microcrystalline
USP-NF: Microcrystalline Cellulose

2 Synonyms

Avicel PH; *Cellets*; *Celex*; cellulose gel; hellulosum microcristallinum; *Celphere*; *Ceolus KG*; crystalline cellulose; E460; *Emcocel*; *Ethispheres*; *Fibrocel*; *MCC Sanaq*; *Pharmacel*; *Tabulose*; *Vivapur*.

3 Chemical Name and CAS Registry Number

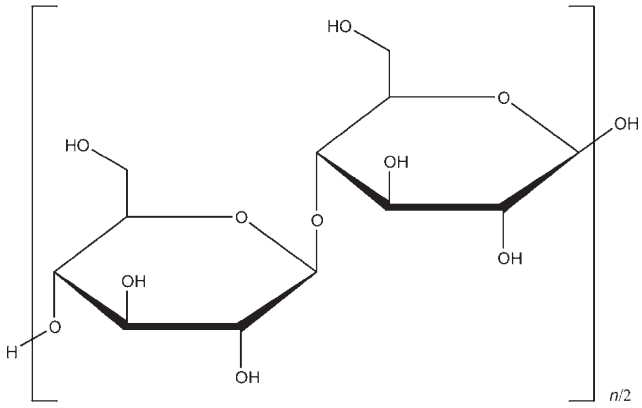
Cellulose [9004-34-6]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ ≈36 000

where $n \approx 220$.

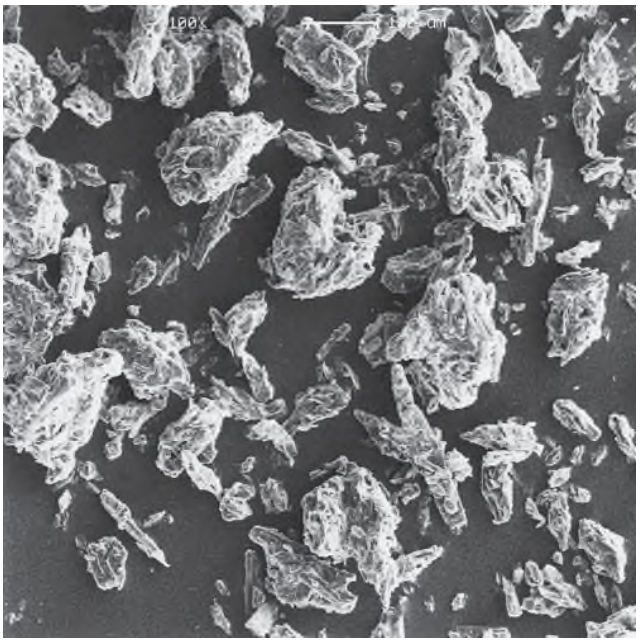
5 Structural Formula



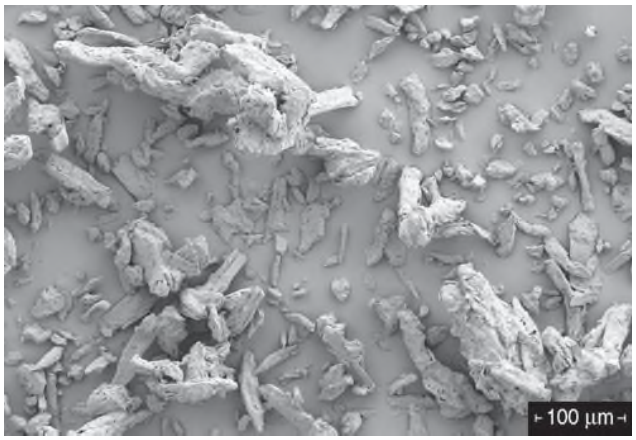
6 Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

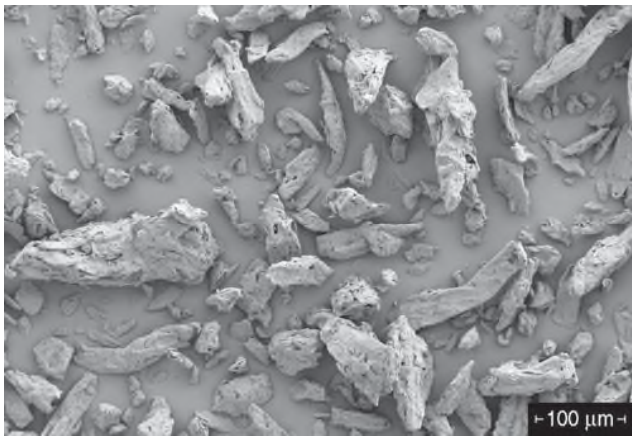
SEM 1: Excipient: microcrystalline cellulose; manufacturer: JRS Pharma LP; lot no.: 98662; magnification: 100×.



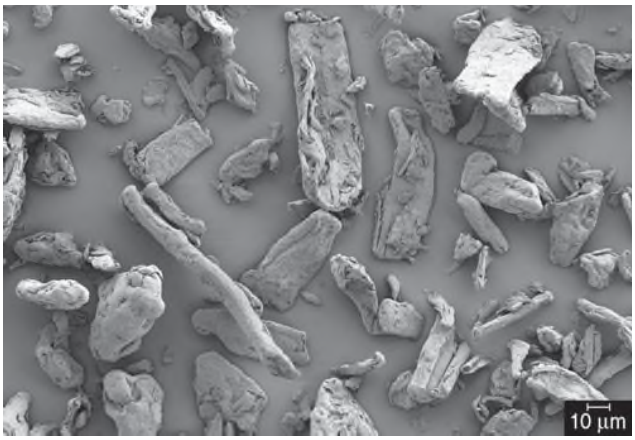
SEM 2: Excipient: microcrystalline cellulose (*Avicel PH-101*); manufacturer: FMC Biopolymer. magnification: 200×; voltage: 3 kV.



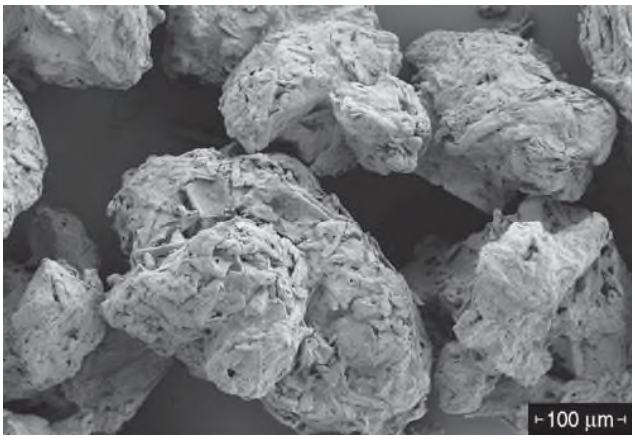
SEM 3: Excipient: microcrystalline cellulose (*Avicel PH-102*); manufacturer: FMC Biopolymer. magnification: 200×; voltage: 3 kV.



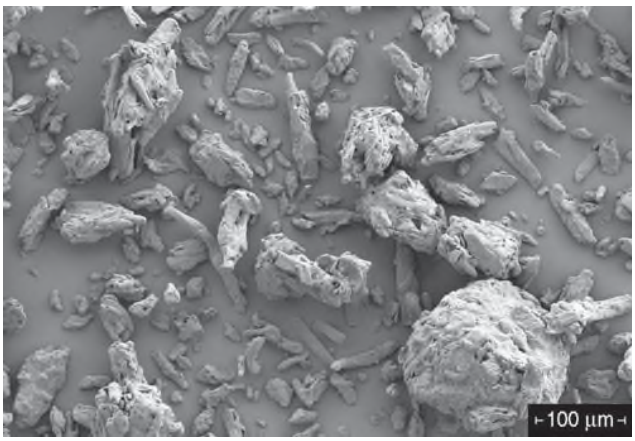
SEM 4: Excipient: microcrystalline cellulose (*Avicel PH-105*); manufacturer: FMC Biopolymer. magnification: 500×; voltage: 3 kV.



SEM 5: Excipient: microcrystalline cellulose (*Avicel PH-200*); manufacturer: FMC Biopolymer. magnification: 200×; voltage: 3 kV.



SEM 6: Excipient: microcrystalline cellulose (*Avicel PH-302*); manufacturer: FMC Biopolymer. magnification: 200×; voltage: 3 kV.



7 Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.[1–7] In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant[8] and disintegrant properties that make it useful in tableting.

Microcrystalline cellulose is also used in cosmetics and food products; *see* Table I.

8 Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Table I: Uses of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

Table II: Pharmacopeial specifications for microcrystalline cellulose.

Test	JP XV	PhEur 6.3	USP32–NF27
Identification	+	+	+
Characters	+	+	–
pH	5.0–7.5	5.0–7.5	5.0–7.5
Bulk density	+	–	+
Loss on drying	⩽7.0%	⩽7.0%	⩽7.0%
Residue on ignition	⩽0.1%	–	⩽0.1%
Conductivity	+	+	+
Sulfated ash	–	⩽0.1%	–
Ether-soluble substances	⩽0.05%	⩽0.05%	⩽0.05%
Water-soluble substances	+	⩽0.25%	⩽0.25%
Heavy metals	⩽10 ppm	⩽10 ppm	⩽0.001%
Microbial limits	+	+	+
Aerobic	$\leqslant 10^3$ cfu/g	$\leqslant 10^3$ cfu/g	$\leqslant 10^3$ cfu/g
Molds and yeasts	$\leqslant 10^2$ cfu/g	$\leqslant 10^2$ cfu/g	$\leqslant 10^2$ cfu/g
Solubility	–	+	–
Particle size distribution	–	–	+

10 Typical Properties

Angle of repose

49° for *Ceolus KG*;

34.4° for *Emcocel 90M*.[9]

Density (bulk)

0.337 g/cm^3;

0.32 g/cm^3 for *Avicel PH-101*;[10]

0.80 ± 5 g/cm^3 for *Cellets 100*, *200*, *350*, *500*, *700*, *1000*;

0.29 g/cm^3 for *Emcocel 90M*;[9]

0.26–0.31 g/cm^3 for *MCC Sanaq 101*;

0.28–0.33 g/cm^3 for *MCC Sanaq 102*;

0.29–0.36 g/cm^3 for *MCC Sanaq 200*;

0.34–0.45 g/cm^3 for *MCC Sanaq 301*;

0.35–0.46 g/cm^3 for *MCC Sanaq 302*;

0.13–0.23 g/cm^3 for *MCC Sanaq UL-002*;

0.29 g/cm^3 for *Vivapur 101*.

Density (tapped)

0.478 g/cm^3;

0.45 g/cm^3 for *Avicel PH-101*;

0.35 g/cm^3 for *Emcocel 90M*.[9]

Density (true) 1.512–1.668 g/cm^3;

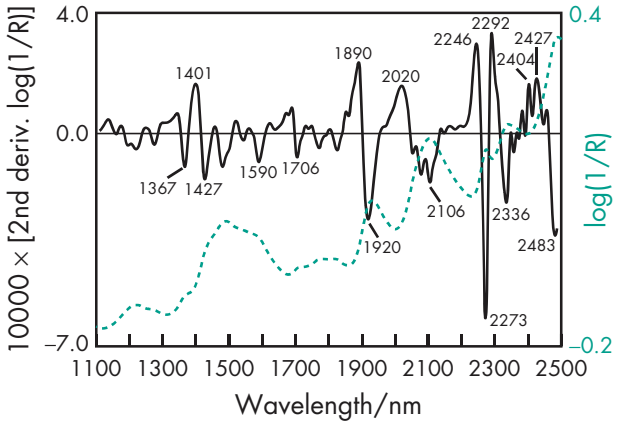


Figure 1: Near-infrared spectrum of cellulose, microcrystalline measured by reflectance.

1.420–1.460 g/cm^3 for *Avicel PH-102*.[11]

Flowability 1.41 g/s for *Emcocel 90M*.[9]

Melting point Chars at 260–270°C.

Moisture content Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.[12] *See* Table III.

NIR spectra *see* Figure 1.

Particle size distribution Typical mean particle size is 20–200 µm. Different grades may have a different nominal mean particle size; *see* Table III.

Solubility Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Specific surface area

1.06–1.12 m^2/g for *Avicel PH-101*;

1.21–1.30 m^2/g for *Avicel PH-102*;

0.78–1.18 m^2/g for *Avicel PH-200*.

11 Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

13 Method of Manufacture

Microcrystalline cellulose is manufactured by controlled hydrolysis with dilute mineral acid solutions of α-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution.

14 Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.[13]

Table III: Properties of selected commercially available grades of microcrystalline cellulose.

Grade	Nominal mean particle size (μm)	Particle size analysis		Moisture content (%)
		Mesh size	Amount retained (%)	
Avicel PH-101 [a]	50	60	⩽1.0	⩽5.0
		200	⩽30.0	
Avicel PH-102 [a]	100	60	⩽8.0	⩽5.0
		200	⩾45.0	
Avicel PH-103 [a]	50	60	⩽1.0	⩽3.0
		200	⩽30.0	
Avicel PH-105 [a]	20	400	⩽1.0	⩽5.0
Avicel PH-112 [a]	100	60	⩽8.0	⩽1.5
Avicel PH-113 [a]	50	60	⩽1.0	⩽1.5
		200	⩽30.0	
Avicel PH-200 [a]	180	60	⩾10.0	⩽5.0
		100	⩾50.0	
Avicel PH-301 [a]	50	60	⩽1.0	⩽5.0
		200	⩽30.0	
Avicel PH-302 [a]	100	60	⩽8.0	⩽5.0
		200	⩾45.0	
Celex 101 [b]	75	60	⩽1.0	⩽5.0
		200	⩾30.0	
Ceolus KG-802 [c]	50	60	⩽0.5	⩽6.0
		200	⩽30.0	
Emcocel 50M [d]	50	60	⩽0.25	⩽5.0
		200	⩽30.0	
Emcocel 90M [d]	91	60	⩽8.0	⩽5.0
		200	⩾45.0	
MCC Sanaq 101[e]	50	60	⩽1.0	⩽6.0
		200	⩽30.0	
MCC Sanaq 102[e]	100	60	⩽8.0	⩽6.0
		200	⩾45.0	
MCC Sanaq 200[e]	180	60	⩾10.0	⩽6.0
		100	⩾50.0	
MCC Sanaq 301[e]	50	60	⩽1.0	⩽6.0
		200	⩾30.0	
MCC Sanaq 302[e]	100	60	⩽8.0	⩽6.0
		200	⩾45.0	
MCC Sanaq UL-002[e]	50	60	<0.5	⩽6.0
		100	<5.0	
		200	<5.0–30.0	
Vivapur 101 [d]	50	60	⩽1.0	⩽5.0
		200	⩽30.0	
Vivapur 102 [d]	90	60	⩽8.0	⩽5.0
		200	⩾45.0	
Vivapur 12 [d]	160	38	⩽1.0	⩽5.0
		94	⩽50.0	

Suppliers:
(a) FMC Biopolymer
(b) International Specialty Products
(c) Asahi Kasei Corporation
(d) JRS Pharma
(e) Pharmatrans Sanaq AG

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK, the workplace exposure limits for cellulose have been set at 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 4 mg/m^3 for respirable dust; the short-term limit for total inhalable dust has been set at 20 mg/m^3.[14]

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (inhalations; oral capsules, powders, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Microcrystalline cellulose and carrageenan; microcrystalline cellulose and carboxymethylcellulose sodium; microcrystalline cellulose and guar gum; powdered cellulose; silicified microcrystalline cellulose.

Microcrystalline cellulose and carrageenan

Synonyms *Lustre Clear.*

Comments *Lustre Clear* (FMC Biopolymer) is an aqueous film coating combining microcrystalline cellulose and carrageenan.

Microcrystalline cellulose and guar gum

Synonyms *Avicel CE-15.*

Comments *Avicel CE-15* (FMC Biopolymer) is a coprocessed mixture of microcrystalline cellulose and guar gum used in chewable tablet formulations.

18 Comments

Microcrystalline cellulose is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

Several different grades of microcrystalline cellulose are commercially available that differ in their method of manufacture,[15,16] particle size, moisture, flow, and other physical properties.[17–29] The larger-particle-size grades generally provide better flow properties in pharmaceutical machinery. Low-moisture grades are used with moisture-sensitive materials. Higher-density grades have improved flowability.

Several coprocessed mixtures of microcrystalline cellulose with other excipients such as carrageenan, carboxymethylcellulose sodium, and guar gum are commercially available; *see* Section 17.

Celphere (Asahi Kasei Corporation) is a pure spheronized microcrystalline cellulose available in several different particle size ranges. *Balocel Sanaq* (Pharmatrans Sanaq AG) is an excipient used mainly in the production of pellets and granulates in direct tableting, which contains lactose, microcrystalline cellulose, and sodium carboxymethylcellulose.

According to PhEur 6.3, microcrystalline cellulose has certain functionality related characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient. Non-mandatory testing procedures have been described for particle size distribution (2.9.31 or 2.9.38) and powder flow (2.9.36).

A specification for microcrystalline cellulose is contained in the Food Chemicals Codex (FCC).[30] The PubChem Compound ID (CID) for microcrystalline cellulose is 14055602.

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21 Author

A Guy.

22 Date of Revision

5 February 2009.

use in parenteral formulations. The degree of substitution of hydroxypropyl groups can vary.

18 Comments

Hydroxypropyl betadex has been investigated as an absorption (permeation) enhancer in oral,[15] transdermal,[16] and nasal[17] systems. It was found to be effective in increasing penetration in some studies, although the mechanism of action may be compound specific.

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W Cook.

22 Date of Revision

27 February 2009.

Hydroxypropyl Cellulose

1 Nonproprietary Names

BP: Hydroxypropylcellulose
JP: Hydroxypropylcellulose
PhEur: Hydroxypropylcellulose
USP-NF: Hydroxypropyl Cellulose

2 Synonyms

Cellulose, hydroxypropyl ether; E463; hydroxypropylcellulosum; hyprolose; *Klucel*; *Nisso HPC*; oxypropylated cellulose.

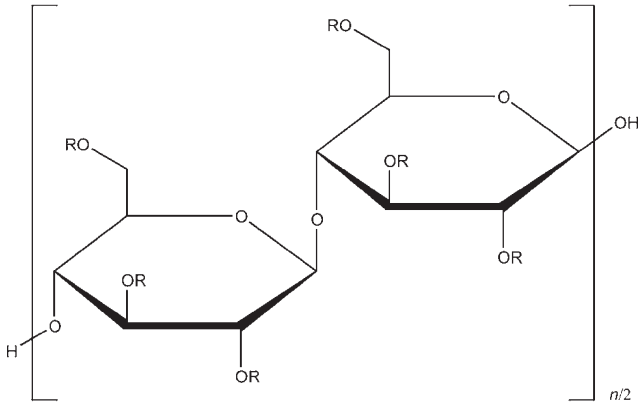
3 Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether [9004-64-2]

4 Empirical Formula and Molecular Weight

The PhEur 6.0 and USP32–NF27 describe hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or another suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades that have various solution viscosities. Molecular weight has a range of 50 000–1 250 000; *see also* Section 10.

5 Structural Formula



R is H or $[CH_2CH(CH_3)O]_mH$ where *m* is a common integral number of cellulose derivatives.

Hydroxypropyl cellulose is an ether of cellulose where some of the hydroxyl groups of the cellulose have been hydroxypropylated forming $-OCH_2CH(OH)CH_3$ groups. The average number of

hydroxyl groups in the glucose ring substituted is referred to as the degree of substitution (DS). Complete substitution would provide a DS of 3.0. Because the hydroxypropyl group added contains a hydroxyl group, this can also be etherified during preparation of hydroxypropyl cellulose. When this occurs, the number of moles of hydroxypropyl groups per glucose ring, or moles of substitution (MS), can be higher than 3. Hydroxypropyl cellulose must have an MS value of approximately 4 in order to have good solubility in water.

6 Functional Category

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations; *see* Table I.

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder,[1] film-coating,[2] and extended-release-matrix former.[3–5] Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes.[6–10] Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release.[11] The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the viscosity of hydroxypropyl cellulose and hence decreases the release rate of a drug. Blends of hydroxypropyl cellulose and other cellulosic polymers have been used to improve wet granulation characteristics and tableting characteristics, as well as to achieve better control and manipulation of the rate of drug release.[12–15] As an alternative technology to wet granulation, dry granulation and direct compression of hydroxypropyl cellulose formulations have been reported to exhibit acceptable tableting and flow characteristics for application in extended-release matrix tablets.[16,17] Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Aqueous solutions containing hydroxypropyl cellulose together with an amount of methyl cellulose or ethanolic solutions have been used.[18–20] Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. Environmental concerns have limited the use of ethanol in film coating solutions. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant; *see* Hydroxypropyl Cellulose, Low-substituted.

Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations.[21–23]

Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

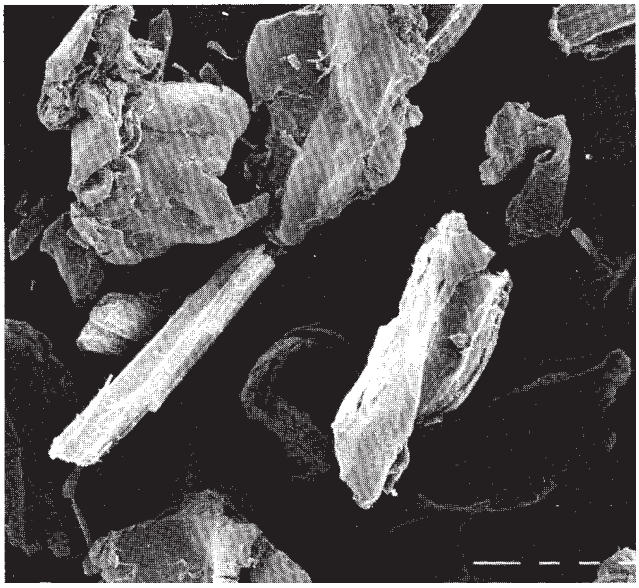
Table I: Typical uses of hydroxypropyl cellulose.

Use	Concentration (%)
Extended release-matrix former	15–35
Tablet binder	2–6
Tablet film coating	5

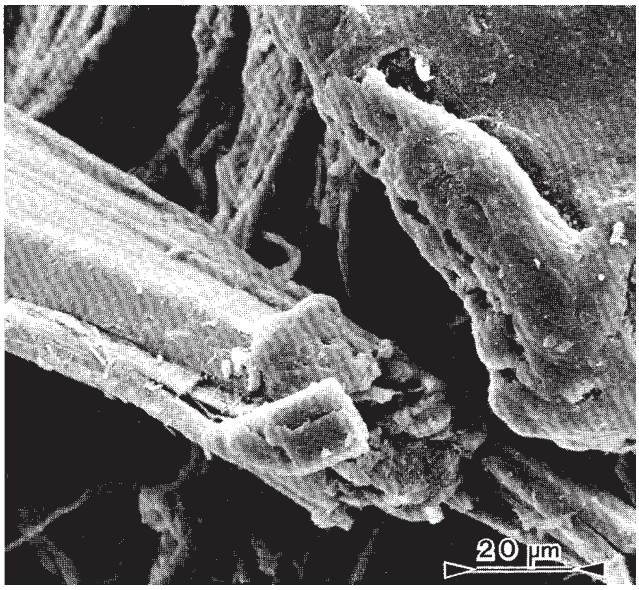
8 Description

Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder. *See also* Section 10.

SEM 1: Excipient: hydroxypropyl cellulose (*Klucel*); manufacturer: Ashland Aqualon Functional Ingredients; magnification: 60×.



SEM 2: Excipient: hydroxypropyl cellulose (*Klucel*); manufacturer: Ashland Aqualon Functional Ingredients; magnification: 600×.



9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

10 Typical Properties

Acidity/alkalinity pH = 5.0–8.5 for a 1% w/w aqueous solution (as stated in PhEur 6.0).

Density (bulk) ≈0.5 g/cm^3

Interfacial tension 12.5 mN/m for a 0.1% w/w aqueous solution compared with mineral oil.

Melting point Softens at 130°C; chars at 260–275°C.

Moisture content Hydroxypropyl cellulose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air. Typical equilibrium moisture content values at 25°C are 4% w/w at 50% relative

Table II: Pharmacopeial specifications for hydroxypropyl cellulose.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	—	+	—
Apparent viscosity	—	+	+
Appearance of solution	+	+	—
pH[a]	5.0–7.5	5.0–8.5	5.0–8.0
Loss on drying	⩽5.0%	⩽7.0%	⩽5.0%
Residue on ignition	⩽0.5%	—	⩽0.2%
Sulfated ash	—	⩽1.6%	—
Arsenic	⩽2 ppm	—	—
Chlorides	⩽0.142%	⩽0.5%	—
Lead	—	—	⩽0.001%
Heavy metals	⩽20 ppm	⩽20 ppm	⩽20 µg/g
Silica	—	⩽0.6%	—
Sulfate	⩽0.048%	—	—
Assay of hydroxypropoxy groups	53.4–77.5%	—	⩽80.5%

(a) pH: 1 g in 50 mL for JPXV; 1 g in 100 g for PhEur 6.0; 1 g in 100 mL for USP32–NF27.

Table III: Moisture content of *Klucel* (Aqualon).

Grade	Molecular weight	Moisture (%)
Klucel EF	≈80 000	0.59
Klucel LF	≈95 000	2.21
Klucel JF	≈140 000	1.44
Klucel GF	≈370 000	1.67
Klucel MF	≈850 000	1.52
Klucel HF	≈1 150 000	4.27

humidity and 12% w/w at 84% relative humidity. *See* Table III. *See also* Figure 1.

NIR spectra *see* Figure 2.

Particle size distribution

Klucel (regular grind), minimum 85% (minimun 80% for *Klucel H* grades) through a US #30 mesh (590 µm), and minimum 99% through a US #20 mesh (840 µm);

Klucel (fine-grind), minimum 99% through a US #60 mesh (250 µm), minimum 90% through a US #80 mesh (177 µm), and minimum 80% through a US #100 mesh (149 µm);

Nisso HPC-L (regular type): 99% through a US #40 mesh sieve (350 µm);

Nisso HPC-L (fine powder type): 99% through a US #100 mesh sieve (150 µm).

Refractive index n_D^{20} = 1.3353 for a 2% w/v aqueous solution.

Solubility

Soluble 1 in 10 parts dichloromethane; 1 in 2.5 parts ethanol (95%); 1 in 2 parts methanol; 1 in 5 parts propan-2-ol; 1 in 5 parts propylene glycol; and 1 in 2 parts water. Practically insoluble in aliphatic hydrocarbons; aromatic hydrocarbons; carbon tetrachloride; petroleum distillates; glycerin; and oils.

Hydroxypropyl cellulose is freely soluble in water below 38°C, forming a smooth, clear, colloidal solution. In hot water, it is insoluble and is precipitated as a highly swollen floc at a temperature between 40 and 45°C. Hydroxypropyl cellulose is soluble in many cold or hot polar organic solvents such as dimethyl formamide; dimethyl sulfoxide; dioxane; ethanol (95%); methanol; propan-2-ol (95%); and propylene glycol. There is no tendency for precipitation in hot organic solvents. However, the grade of hydroxypropyl cellulose can have a marked effect upon solution quality in some organic liquids that are borderline solvents, such as acetone; butyl acetate; cyclohexanol; dichloromethane; lactic acid; methyl acetate; methyl ethyl ketone; propan-2-ol (99%); and *tert*-butanol.

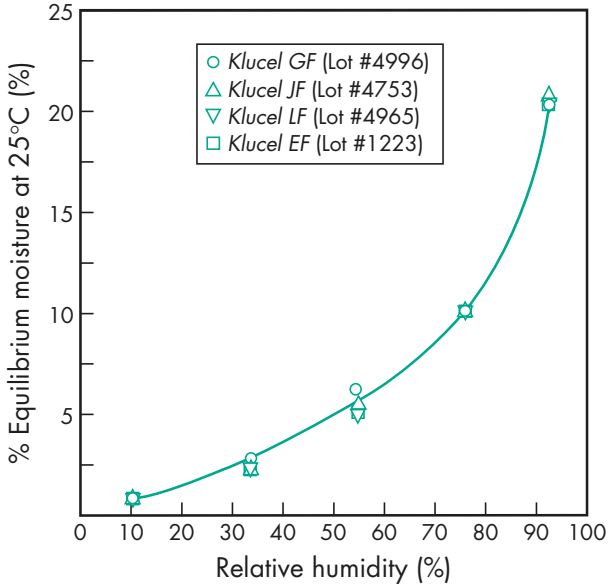


Figure 1: Equilibrium moisture content of various grades of hydroxypropyl cellulose (*Klucel*, Ashland Aqualon Functional Ingredients).

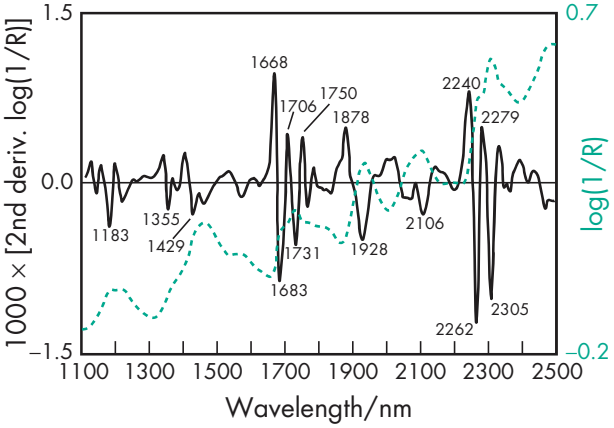


Figure 2: Near-infrared spectrum of hydroxypropyl cellulose measured by reflectance.

The higher-viscosity grades of hydroxypropyl cellulose tend to produce slightly inferior solutions. However, the solution quality in borderline solvents can often be greatly improved by the use of small quantities (5–15%) of a cosolvent. For example, dichloromethane is a borderline solvent for *Klucel HF* and solutions have a granular texture, but a smooth solution may be produced by adding 10% methanol.

Hydroxypropyl cellulose is compatible with a number of high-molecular-weight, high-boiling waxes and oils, and can be used to modify certain properties of these materials. Examples of materials that are good solvents for hydroxypropyl cellulose at an elevated temperature are acetylated monoglycerides, glycerides, pine oil, polyethylene glycol, and polypropylene glycol.

Specific gravity 1.2224 for particles; 1.0064 for a 2% w/v aqueous solution at 20°C.

Surface tension *see* Table IV.

Viscosity (dynamic) A wide range of viscosity types are commercially available; *see* Table V. Solutions should be prepared by gradually adding the hydroxypropyl cellulose to a vigorously stirred solvent. Increasing concentration produces solutions of increased viscosity. *See also* Section 11 for information on solution stability.

H

Table IV: Surface tension (mN/m) of aqueous solutions of *Nisso HPC* (Nippon Soda Co. Ltd.) at 20°C.

Grade	Surface tension (mN/m) at 20°C for aqueous solutions of stated concentration			
	0.01%	0.1%	1.0%	10.0%
Nisso HPC-L	51.0	49.1	46.3	45.8
Nisso HPC-M	54.8	49.7	46.3	—

Table V: Viscosity of aqueous solutions of *Klucel* (Ashland Aqualon Functional Ingredients) at 25°C.

Grade	Viscosity (mPa s) of various aqueous solutions of stated concentration			
	1%	2%	5%	10%
Klucel HF	1500–3000	—	—	—
Klucel MF	—	4000–6500	—	—
Klucel GF	—	150–400	—	—
Klucel JF	—	—	150–400	—
Klucel LF	—	—	75–150	—
Klucel EF	—	—	—	200–600

11 Stability and Storage Conditions

Hydroxypropyl cellulose powder is a stable material, although it is hygroscopic after drying.

Aqueous solutions of hydroxypropyl cellulose are stable at pH 6.0–8.0, with the viscosity of solutions being relatively unaffected. However, at low pH aqueous solutions may undergo acid hydrolysis, resulting in chain scission and hence a decrease in solution viscosity. The rate of hydrolysis increases with increasing temperature and hydrogen ion concentration. At high pH, alkali-catalyzed oxidation may degrade the polymer and result in a decrease in viscosity of solutions. This degradation can occur owing to the presence of dissolved oxygen or oxidizing agents in a solution.

Increasing temperature causes the viscosity of aqueous solutions to decrease gradually until the viscosity drops suddenly at about 45°C owing to the limited solubility of hydroxypropyl cellulose. However, this process is reversible and on cooling the original viscosity is restored.

The high level of substitution of hydroxypropyl cellulose improves the resistance of the polymer to degradation by molds and bacteria.[20] However, aqueous solutions are susceptible to degradation under severe conditions and a viscosity decrease may occur. Certain enzymes produced by microbial action will degrade hydroxypropyl cellulose in solution.[24] Therefore, for prolonged storage, an antimicrobial preservative should be added to aqueous solutions. Solutions of hydroxypropyl cellulose in organic solvents do not generally require preservatives.

Ultraviolet light will also degrade hydroxypropyl cellulose and aqueous solutions may therefore decrease slightly in viscosity if exposed to light for several months.

Aqueous hydroxypropyl cellulose solutions have optimum stability when the pH is maintained at 6.0–8.0, and also when the solution is protected from light, heat, and the action of micro-organisms.

Hydroxypropyl cellulose powder should be stored in a well-closed container in a cool, dry place.

Table VI: Compatibility of hydroxypropyl cellulose (*Nisso HPC*) with inorganic salts in aqueous solutions.[a]

Salt	Concentration of salt (% w/w)						
	2	3	5	7	10	30	50
Aluminum sulfate	S	S	I	I	I	I	I
Ammonium nitrate	S	S	S	S	S	I	I
Ammonium sulfate	S	S	I	I	I	I	I
Calcium chloride	S	S	S	S	S	T	I
Dichromic acid	S	S	S	S	S	S	S
Disodium hydrogenphosphate	S	S	I	I	I	I	I
Ferric chloride	S	S	S	S	S	I	I
Potassium ferrocyanide	S	S	S	I	I	I	I
Silver nitrate	S	S	S	S	S	S	T
Sodium acetate	S	S	S	S	I	I	I
Sodium carbonate	S	S	I	I	I	I	I
Sodium chloride	S	S	S	S	I	I	I
Sodium nitrate	S	S	S	S	S	I	I
Sodium sulfate	S	S	I	I	I	I	I
Sodium sulfite	S	S	I	I	I	I	I
Sodium thiosulfate	T	T	T	I	I	I	I

(a) S, completely soluble; T, turbid white; I, insoluble.

12 Incompatibilities

Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulose solutions.

The compatibility of hydroxypropyl cellulose with inorganic salts varies depending upon the salt and its concentration; *see* Table VI. Hydroxypropyl cellulose may not tolerate high concentrations of other dissolved materials.

The balance of the hydrophilic–lipophilic properties of the polymer, which are required for dual solubility, reduces its ability to hydrate with water and it therefore tends to be salted out in the presence of high concentrations of other dissolved materials.

The precipitation temperature of hydroxypropyl cellulose is lower in the presence of relatively high concentrations of other dissolved materials that compete for the water in the system; *see* Table VII.

Table VII: Variation in precipitation temperature of hydroxypropyl cellulose (*Klucel H*) in the presence of other materials.

Ingredients and concentrations	Precipitation temperature (°C)
1% *Klucel H*	41
1% *Klucel H* + 1.0% sodium chloride	38
1% *Klucel H* + 5.0% sodium chloride	30
0.5% *Klucel H* + 10% sucrose	41
0.5% *Klucel H* + 30% sucrose	32
0.5% *Klucel H* + 40% sucrose	20
0.5% *Klucel H* + 50% sucrose	*7*

13 Method of Manufacture

A purified form of cellulose is reacted with sodium hydroxide to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then reacted with propylene oxide at elevated temperature and pressure. The propylene oxide can be substituted on the cellulose through an ether linkage at the three reactive hydroxyls present on each anhydroglucose monomer unit of the cellulose chain. Etherification takes place in such a way that hydroxypropyl substituent groups contain almost entirely secondary hydroxyls. The secondary hydroxyl present in the side chain is available for further reaction with the propylene oxide, and 'chaining-out' may take place. This

results in the formation of side chains containing more than 1 mole of combined propylene oxide.

14 Safety

Hydroxypropyl cellulose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hydroxypropyl cellulose is generally regarded as an essentially nontoxic and nonirritant material.[25,26] It is not absorbed from the gastrointestinal tract and is fully recovered in feces after oral administration in rats. It does not exhibit skin irritation or skin sensitization. However, the use of hydroxypropyl cellulose as a solid ocular insert has been associated with rare reports of discomfort or irritation, including hypersensitivity and edema of the eyelids. Adverse reactions to hydroxypropyl cellulose are rare. However, it has been reported that a single patient developed contact dermatitis due to hydroxypropyl cellulose in a transdermal estradiol patch.[27]

The WHO has specified an acceptable daily intake for hydroxypropyl cellulose of up to 1500 mg/kg body-weight.[28] Excessive consumption of hydroxypropyl cellulose may have a laxative effect.

LD_{50} (rat, IV): 0.25 g/kg[29]

LD_{50} (rat, oral): 10.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hydroxypropyl cellulose dust may be irritant to the eyes; eye protection is recommended. Excessive dust generation should be avoided to minimize the risk of explosions.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (oral capsules and tablets; topical and transdermal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Hydroxyethyl cellulose; hydroxypropyl cellulose, low-substituted; hypromellose.

18 Comments

Hydroxypropyl cellulose is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

Hydroxypropyl cellulose is a thermoplastic polymer that can be processed by virtually all fabrication methods used for plastics.

It is also used in hot-melt extruded films for topical use. When it is produced with chlorpheniramine maleate, the matrix is stabilized, allowing film processing at lower temperatures.[30] Mucoadhesive hydroxypropyl cellulose microspheres have been prepared for powder inhalation preparations.[31]

A specification for hydroxypropyl cellulose is included in the Food Chemicals Codex (FCC).[32]

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MA Kabir, JP Reo.

22 Date of Revision

23 February 2009.

H

Hydroxypropyl Cellulose, Low-substituted

1 Nonproprietary Names

JP: Low Substituted Hydroxypropylcellulose

USP-NF: Low-Substituted Hydroxypropyl Cellulose

2 Synonyms

Cellulose, 2-hydroxypropyl ether; 2-hydroxypropyl ether (low-substituted) cellulose; hyprolose, low-substituted; *L-HPC*; oxypropylated cellulose.

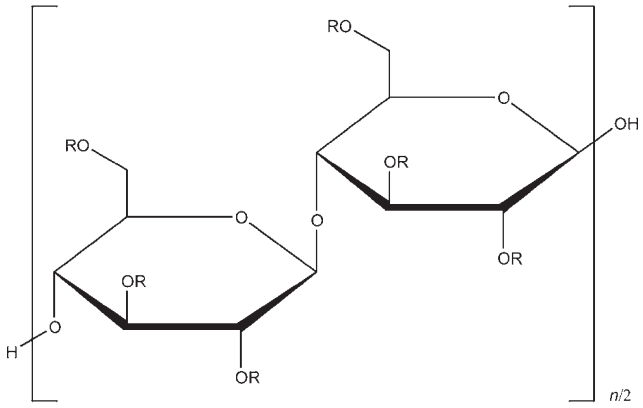
3 Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether (low-substituted) [9004-64-2]

4 Empirical Formula and Molecular Weight

The USP32–NF27 describes low-substituted hydroxypropyl cellulose as a low-substituted hydroxypropyl ether of cellulose. Compared to hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose has only a small proportion of the three free hydroxyl groups per glucose subunit converted to a hydroxypropyl ether.[1] When dried at 105°C for 1 hour, it contains not less than 5.0% and not more than 16.0% of hydroxypropoxy groups (—$OCH_2CHOHCH_3$). Low-substituted hydroxypropyl cellulose is commercially available in a number of different grades that have different particle sizes and substitution levels.

5 Structural Formula



R is H or $[CH_2CH(CH_3)O]_mH$

6 Functional Category

Tablet and capsule disintegrant; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Low-substituted hydroxypropyl cellulose is widely used in oral solid-dosage forms. It is primarily used as a disintegrant, and as a binder for tablets and granules in wet or dry granulation.[1] It has been used in the preparation of rapidly disintegrating tablets produced by direct compression methods.[2–4] In addition, low-substituted hydroxypropyl cellulose has been used as a binder/disintegrant included in the powder layering process on spherical cores and to prepare pellets by extrusion/spheronization.[1,6,7] A low particle size and high hydroxypropyl content is recommended to produce round spheres and rapid dissolution.[1,5]

There are a number of grades that have different particle sizes and substitution levels. *LH-11* has the longest fibrous particles, and

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SA Shah, D Thassu.

22 Date of Revision

8 October 2008.

Hypromellose

H

1 Nonproprietary Names

BP: Hypromellose
JP: Hypromellose
PhEur: Hypromellose
USP: Hypromellose

2 Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; hypromellosum; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; MHPC; *Pharmacoat*; *Tylopur*; *Tylose MO*.

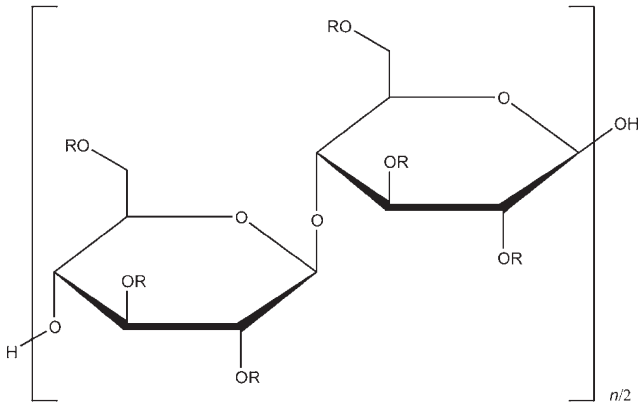
3 Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

4 Empirical Formula and Molecular Weight

The PhEur 6.3 describes hypromellose as a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP 32 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g. hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CH(OH)CH_3$), calculated on a dried basis. It contains methoxy and hydroxypropoxy groups conforming to the limits for the various types of hypromellose; *see* Section 9. Molecular weight is approximately 10 000–1 500 000.

5 Structural Formula



where R is H, CH_3, or $CH_3CH(OH)CH_2$

6 Functional Category

Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder,[1] in film-coating,[2–7] and as a matrix for use in extended-release tablet formulations.[8–12] Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.[13]

Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while

higher-viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include *AnyCoat C*, *Spectracel*, *Pharmacoat*, and the *Methocel E Premium LV* series.

Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undissolved fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%.[13]

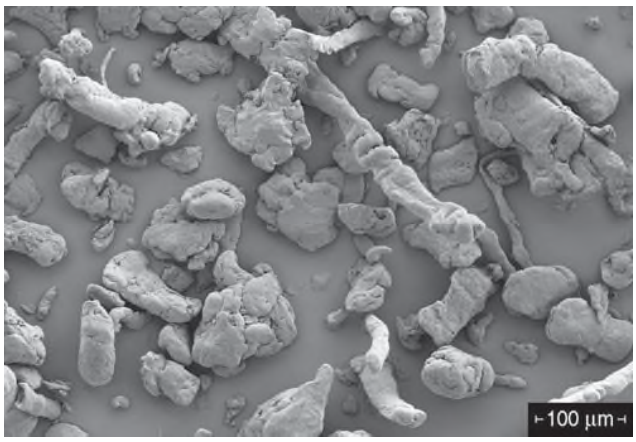
Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

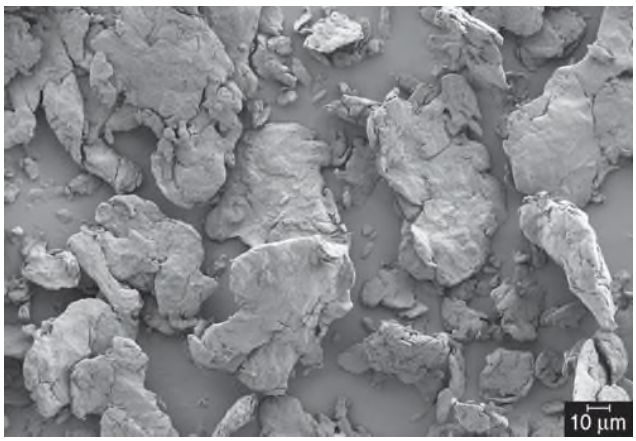
8 Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder. *See also* Section 10.

SEM 1: Excipient: *Methocel E5*; manufacturer: Dow Wolff Cellulosics; magnification: 200×; voltage: 3 kV.



SEM 2: Excipient: *Methocel K4M*; manufacturer: Dow Wolff Cellulosics; magnification: 500×; voltage: 3 kV.



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for hypromellose.

Test	JP XV	PhEur 6.3	USP 32
Identification	+	+	+
Characters	—	+	—
Appearance of solution	—	+	—
pH (2% w/w solution)	5.0–8.0	5.0–8.0	5.0–8.0
Apparent viscosity	+	+[a]	+
<600 mPa s	80–120%	80–120%	80–120%
⩾600 mPa s	75–140%	75–140%	75–140%
Loss on drying	⩽5.0%	⩽5.0%	⩽5.0%
Residue on ignition	⩽1.5%	—	⩽1.5%
Sulfated ash	—	⩽1.5%	—
Heavy metals	⩽20 ppm	⩽20 ppm	⩽20 ppm
Methoxy content	+	+[a]	+
Type 1828	16.5–20.0%	16.5–20.0%	16.5–20.0%
Type 2208	19.0–24.0%	19.0–24.0%	19.0–24.0%
Type 2906	27.0–30.0%	27.0–30.0%	27.0–30.0%
Type 2910	28.0–30.0%	28.0–30.0%	28.0–30.0%
Hydroxypropoxy content	+	+[a]	+
Type 1828	23.0–32.0%	23.0–32.0%	23.0–32.0%
Type 2208	4.0–12.0%	4.0–12.0%	4.0–12.0%
Type 2906	4.0–7.5%	4.0–7.5%	4.0–7.5%
Type 2910	7.0–12.0%	7.0–12.0%	7.0–12.0%

(a) May be a functionality related characteristic.

10 Typical Properties

Acidity/alkalinity pH = 5.0–8.0 for a 2% w/w aqueous solution.
Ash ⩽1.5%
Autoignition temperature 360°C
Density (bulk) 0.341 g/cm^3
Density (tapped) 0.557 g/cm^3
Density (true) 1.326 g/cm^3
Melting point Browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.
Moisture content Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air. *See* Figure 1.
NIR spectra *see* Figure 2.
Solubility Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. Some grades are swellable in ethanol.[14] *See also* Section 11.
Specific gravity 1.26
Viscosity (dynamic)

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions; *see* Table II.

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of the required amount of water. The water should be vigorously stirred and heated to 80–90°C, and then the hypromellose should be added. The heat source can be removed once the hypromellose has been thoroughly dispersed into the hot water. Sufficient cold water should then be added to produce the required volume while continuing to stir.

H

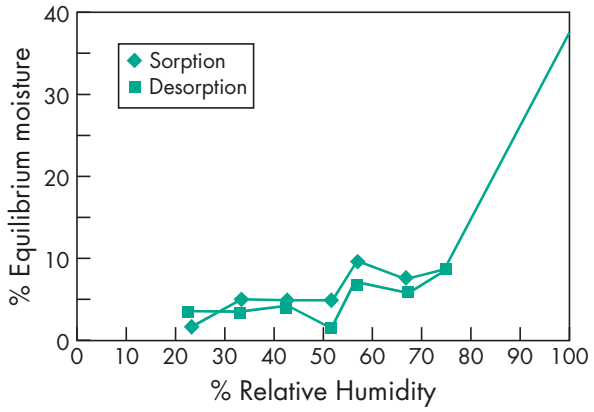


Figure 1: Absorption–desorption isotherm for hypromellose.

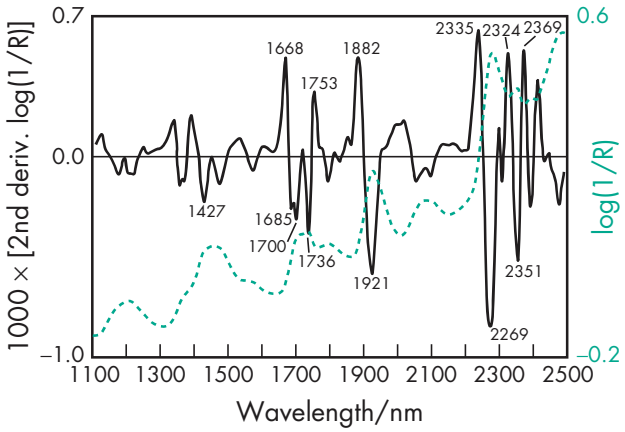


Figure 2: Near-infrared spectrum of hypromellose measured by reflectance.

When aqueous/organic cosolvent mixtures are used for solution preparation, hypromellose should first be dispersed into the organic solvent at a ratio of 5–8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the final volume. Examples of suitable water-miscible organic solvents include ethanol and glycols. A similar preparation procedure should be used when ethanol and dichloromethane constitute a completely organic cosolvent mixture.

11 Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying.

Solutions are stable at pH 3–11. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gelation temperature is 50–90°C, depending upon the grade and concentration of material. For temperatures below the gelation temperature, viscosity of the solution decreases as temperature is increased. Beyond the gelation temperature, viscosity increases as temperature is increased.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.[15] However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Table II: Typical viscosity values for 2% (w/v) aqueous solutions of *Methocel* (Dow Wolff Cellulosics) and *Metolose* (Shin-Etsu Chemical Co. Ltd.). Viscosities measured at 20°C.

Methocel and *Metolose* products	JP/PhEur/ USP designation	Nominal viscosity (mPa s)
Methocel K3 Premium LV	2208	3
Methocel K100 Premium LVEP	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15 000
Methocel K100M Premium	2208	100 000
Methocel E3 Premium LV	2910	3
Methocel E5 Premium LV	2910	5
Methocel E6 Premium LV	2910	6
Methocel E15 Premium LV	2910	15
Methocel E50 Premium LV	2910	50
Methocel E4M Premium	2910	4000
Methocel E10M Premium CR	2910	10 000
Methocel F50 Premium	2906	50
Methocel F4M Premium	2906	4000
Metolose 60SH	2910	50, 4000, 10 000
Metolose 65SH	2906	50, 400, 1500, 4000
Metolose 90SH	2208	100, 400, 4000, 15 000

12 Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

13 Method of Manufacture

A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules. Hypromellose can then be exposed to anhydrous hydrogen chloride to induce depolymerization, thus producing low viscosity grades.

14 Safety

Hypromellose is widely used as an excipient in oral, opthalmic, nasal, and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hypromellose is generally regarded as a nontoxic and nonirritating material, although excessive oral consumption may have a laxative effect.[16] The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.[17] In fact, high dosages of hypromellose are being investigated for treating various metabolic syndromes.[18,19]

LD_{50} (mouse, IP): 5 g/kg[20]

LD_{50} (rat, IP): 5.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritating to the eyes, so eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (ophthalmic and nasal preparations; oral capsules, suspensions, syrups, and tablets;

topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Ethylcellulose; hydroxyethyl cellulose; hydroxyethylmethyl cellulose; hydroxypropyl cellulose; hypromellose acetate succinate; hypromellose phthalate; methylcellulose.

18 Comments

Hypromellose has been used in pharmaceutical dosage forms produced using hot-melt extrusion.[21] Premix coating formulations which contain hypromellose as a film-forming agent include *Opadry* (Colorcon) and *Advantia* Prime Coating Systems (ISP). *Methocel* K4MP DC and *Methocel* K100MP DC (Dow Wolff Cellulosics); they have been developed and commercialized to facilitate direct compression of tablets exhibiting modified-release performance.

Powdered or granular, surface-treated grades of hypromellose are also available that are dispersible in cold water. These are not recommended for oral use.

A specification for hypromellose is contained in the Food Chemicals Codex (FCC).[22]

The PubChem Compound ID (CID) for hypromellose is 24832095.

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TL Rogers.

22 Date of Revision

20 February 2009.

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ME Quinn, PJ Sheskey.

22 Date of Revision

17 February 2009.

Povidone

1 Nonproprietary Names

BP: Povidone
JP: Povidone
PhEur: Povidone
USP: Povidone

2 Synonyms

E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; povidonum; *Povipharm*; PVP; 1-vinyl-2-pyrrolidinone polymer.

3 Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4 Empirical Formula and Molecular Weight

$(C_6H_9NO)_n$ 2500–3 000 000

The USP 32 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a *K*-value, in the range 10–120. The *K*-value is calculated using Fikentscher's equation:[1]

$$\log z = c\left[\frac{75k^2}{1+1.5kc}\right]+k$$

where z is the relative viscosity of the solution of concentration c (in % w/v), and k is the *K*-value $\times 10^{-3}$. Alternatively, the *K*-value may be determined from the following equation:

$$K\text{-value} = \sqrt{\frac{300c\log z\,(c+1.5c\log z)^2+1.5}{0.15c+0.003c^2}}$$

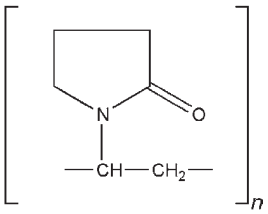
where z is the relative viscosity of the solution of concentration c (in % w/v). Approximate molecular weights for different povidone grades are shown in Table I.

Table I: Approximate molecular weights for different grades of povidone.

K-value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

See also Section 8.

5 Structural Formula



6 Functional Category

Disintegrant; dissolution enhancer; suspending agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.[2,3] Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.[4–6] Povidone solutions may also be used as coating agents or as binders when coating active pharmaceutical ingredients on a support such as sugar beads.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly

soluble active drugs may be increased by mixing with povidone. *See* Table II.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations; *see* Section 14.

Table II: Uses of povidone.

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

8 Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with *K*-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher *K*-value povidones are manufactured by drum drying and occur as plates.

9 Pharmacopeial Specifications

See Table III. *See also* Section 18.

10 Typical Properties

Acidity/alkalinity pH = 3.0–7.0 (5% w/v aqueous solution); pH = 4.0–7.0 (5% w/v aqueous solution) for *Povipharm K90*.

Density (bulk) 0.29–0.39 g/cm^3 for *Plasdone*.

Density (tapped) 0.39–0.54 g/cm^3 for *Plasdone*.

Density (true) 1.180 g/cm^3

Flowability

20 g/s for povidone K-15;

16 g/s for povidone K-29/32.

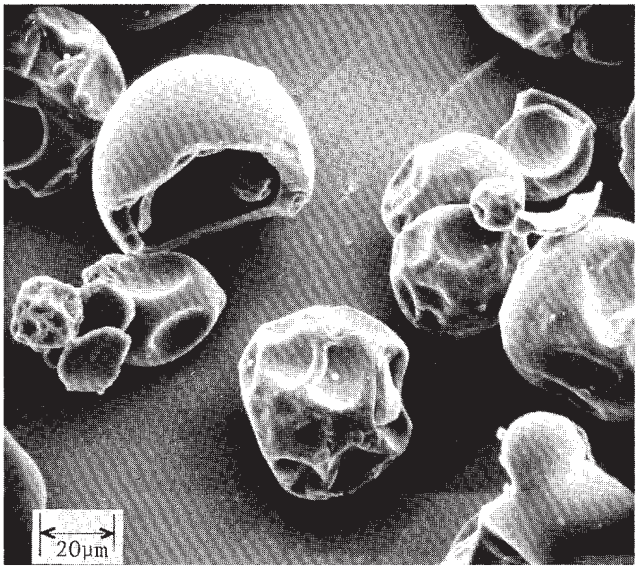
Melting point Softens at 150°C.

Moisture content Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities. *See* Figures 1 and 2.

NIR spectra *see* Figure 3.

SEM 1: Excipient: povidone K-15 (*Plasdone K-15*); manufacturer: ISP; lot no.: 82A-1; magnification: 60×; voltage: 5 kV.

SEM 2: Excipient: povidone K-15 (*Plasdone K-15*); manufacturer: ISP; lot no.: 82A-1; magnification: 600×; voltage: 5 kV.



SEM 3: Excipient: povidone K-26/28 (*Plasdone K-26/28*); manufacturer: ISP; lot no.: 82A-2; magnification: 60×; voltage: 5 kV.

Particle size distribution

Kollidon 25/30: 90% >50 μm, 50% >100 μm, 5% >200 μm;

Kollidon 90: 90% >200 μm, 95% >250 μm.[7]

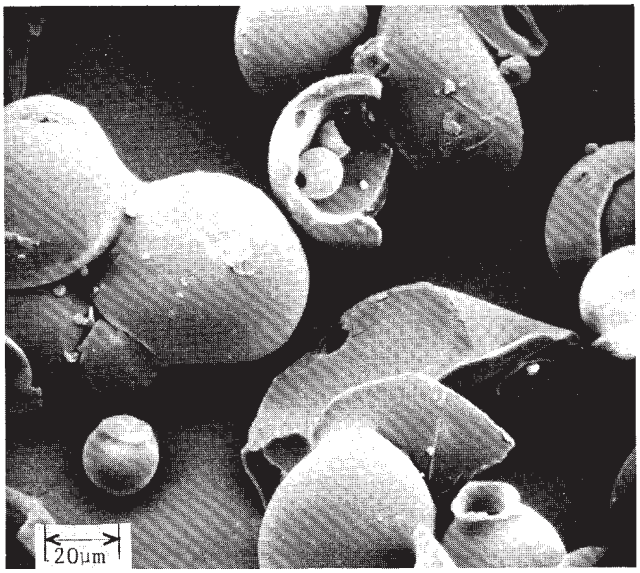
Solubility Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the *K*-value.

Viscosity (dynamic) The viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed. *See* Tables IV and V.[7]

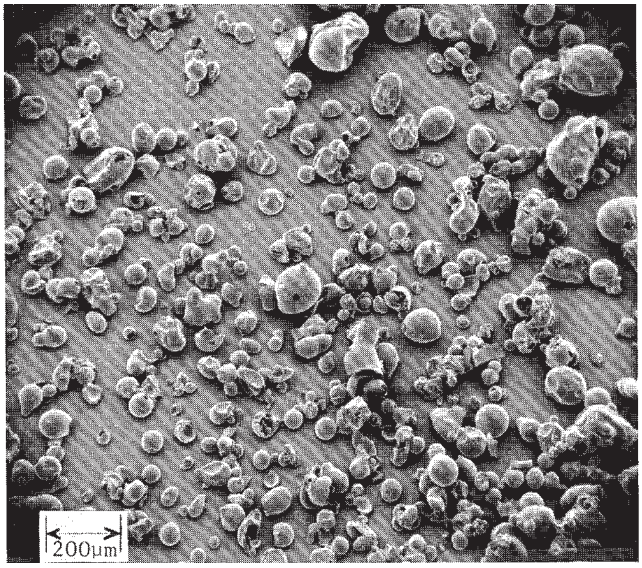
11 Stability and Storage Conditions

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are

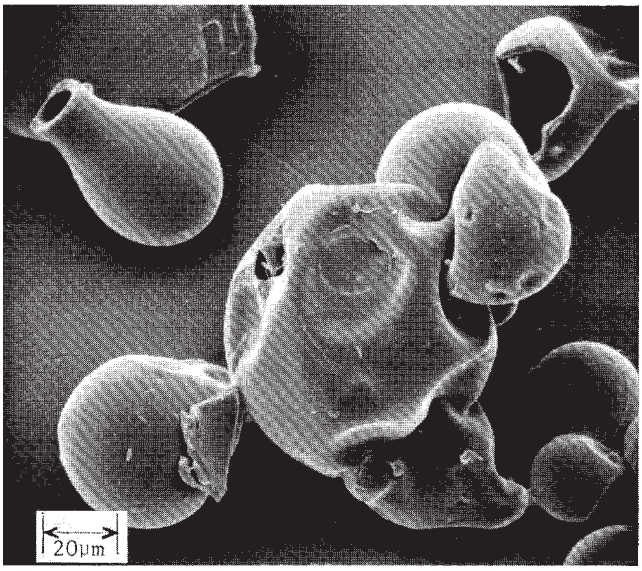
SEM 4: Excipient: povidone K-26/28 (*Plasdone K-26/28*); manufacturer: ISP; lot no.: 82A-2; magnification: 600×; voltage: 10 kV.



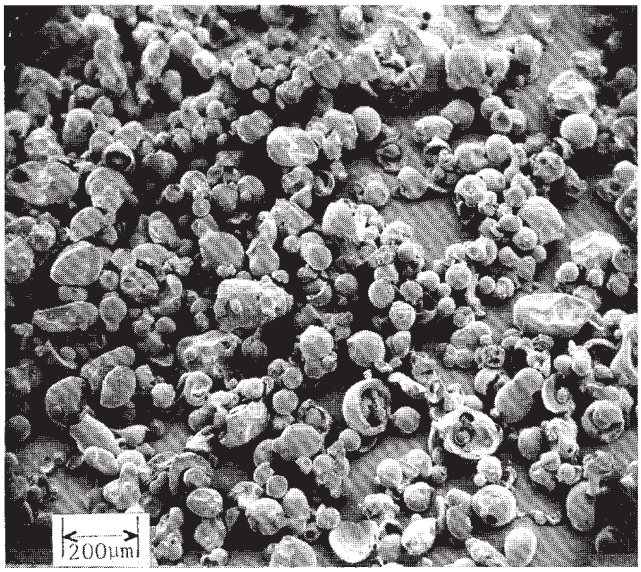
SEM 5: Excipient: povidone K-30 (*Plasdone K-30*); manufacturer: ISP; lot no.: 82A-4; magnification: 60×; voltage: 10 kV.



SEM 6: Excipient: povidone K-30 (*Plasdone K-30*); manufacturer: ISP; lot no.: 82A-4; magnification: 600×; voltage: 10 kV.



SEM 7: Excipient: povidone K-29/32 (*Plasdone K-29/32*); manufacturer: ISP; lot no.: 82A-3; magnification: 60×; voltage: 5 kV.



susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds; *see* Section 18. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

13 Method of Manufacture

Povidone is manufactured by the Reppe process. Acetylene and formaldehyde are reacted in the presence of a highly active copper acetylide catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer, vinylpyrrolidone, is then polymerized in the presence of a combination of catalysts to produce povidone.

14 Safety

Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.[8]

SEM 8: Excipient: povidone K-29/32 (*Plasdone K-29/32*); manufacturer: ISP; lot no.: 82A-3; magnification: 600×; voltage: 10 kV.

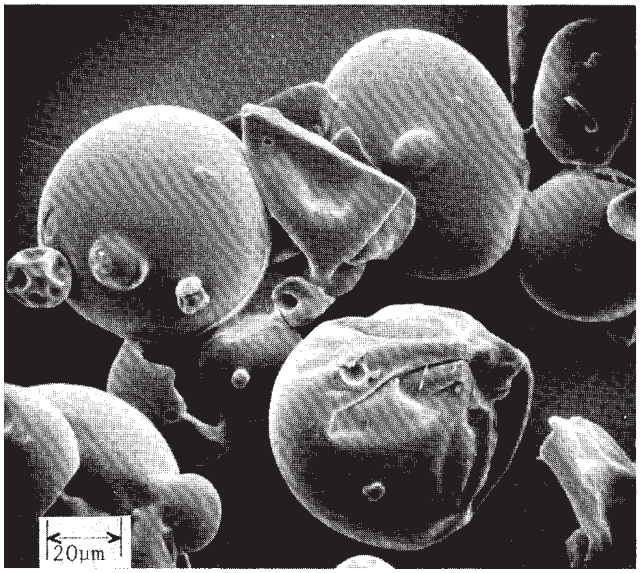


Table III: Pharmacopeial specifications for povidone.

Test	JP XV	PhEur 6.5	USP 32
Identification	+	+	+
Characters	–	+	–
pH	+	+	3.0–7.0
$K \leqslant 30$	3.0–5.0	3.0–5.0	–
$K > 30$	4.0–7.0	4.0–7.0	–
Appearance of solution	+	+	–
Viscosity	–	+	–
Water	⩽5.0%	⩽5.0%	⩽5.0%
Residue on ignition	⩽0.1%	⩽0.1%	⩽0.1%
Lead	–	–	⩽10 ppm
Aldehydes	⩽500 ppm[a]	⩽500 ppm[a]	⩽0.05%
Formic acid	–	+	–
Hydrazine	⩽1 ppm	⩽1 ppm	⩽1 ppm
Vinylpyrrolidinone	⩽10 ppm	⩽10 ppm	⩽0.001%
Pyrrolidone	–	⩽3.0%	–
Peroxides	⩽400 ppm[b]	⩽400 ppm[b]	–
K-value	25–90	–	–
⩽15	90.0–108.0%	85.0–115.0%	85.0–115.0%
>15	90.0–108.0%	90.0–108.0%	90.0–108.0%
Heavy metals	⩽10 ppm	⩽10 ppm	–
Assay (nitrogen content)	11.5–12.8%	11.5–12.8%	11.5–12.8%

(a) Expressed as acetaldehyde.
(b) Expressed as hydrogen peroxide.

Table IV: Dynamic viscosity of 10% w/v aqueous povidone (*Kollidon*) solutions at 20°C.[7]

Grade	Dynamic viscosity (mPa s)
K-11/14	1.3–2.3
K-16/18	1.5–3.5
K-24/27	3.5–5.5
K-28/32	5.5–8.5
K-85/95	300–700

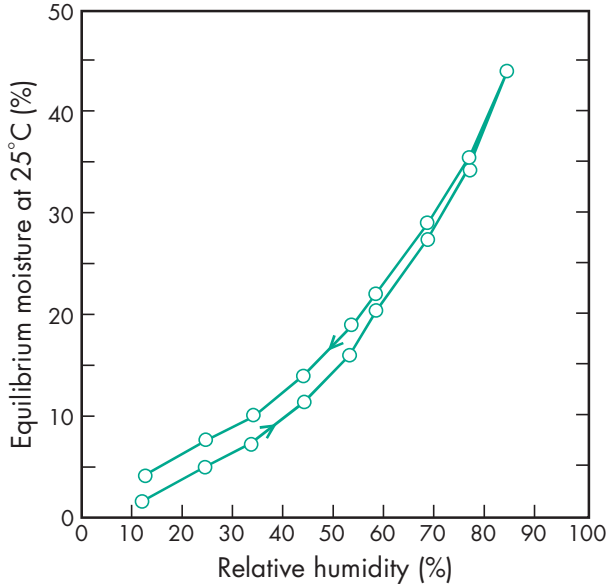


Figure 1: Sorption–desorption isotherm of povidone K-15 (*Plasdone K-15*, ISP).

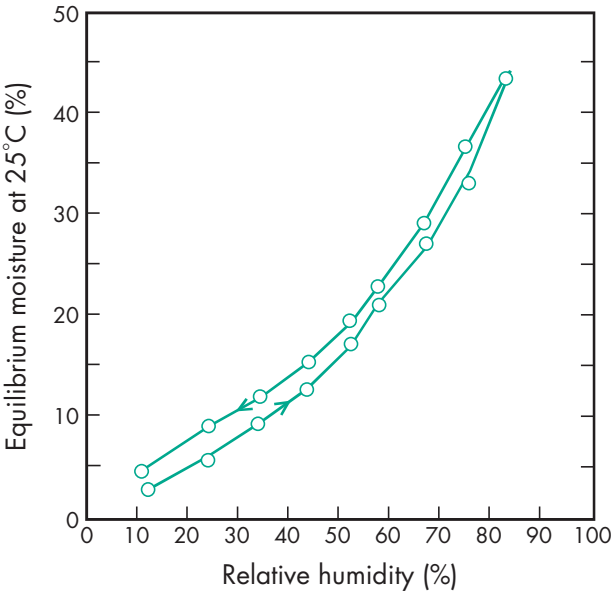


Figure 2: Sorption–desorption isotherm of povidone K-29/32 (*Plasdone K-29/32*, ISP).

Table V: Dynamic viscosity of 5% w/v povidone (*Kollidon*) solutions in ethanol (95%) and propan-2-ol at 25°C.[7]

Grade	Dynamic viscosity (mPa s)	
	Ethanol (95%)	Propan-2-ol
K-12PF	1.4	2.7
K-17PF	1.9	3.1
K-25	2.7	4.7
K-30	3.4	5.8
K-90	53.0	90.0

Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes.[8] Povidone additionally has no irritant effect on the skin and causes no sensitization.

Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with povidone.[9] Evidence also

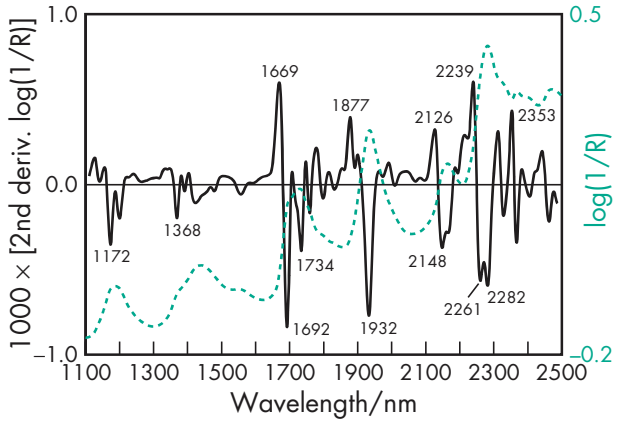


Figure 3: Near-infrared spectrum of povidone measured by reflectance.

exists that povidone may accumulate in the organs of the body following intramuscular injection.[10]

A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.[11]

LD_{50} (mouse, IP): 12 g/kg[12]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Accepted for use in Europe as a food additive. Included in the FDA Inactive Ingredients Database (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspensions, and tablets; sublingual tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Crospovidone.

18 Comments

Povidone is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

The molecular adduct formation properties of povidone may be used advantageously in solutions, slow-release solid-dosage forms, and parenteral formulations. Perhaps the best-known example of povidone complex formation is povidone–iodine, which is used as a topical disinfectant.

For accurate standardization of solutions, the water content of the solid povidone must be determined before use and taken into account for any calculations. Many excipients such as povidone may contain peroxides as trace contaminants. These can lead to degradation of an active pharmaceutical ingredient that is sensitive to oxidation.

A specification for povidone is contained in the Food Chemicals Codex (FCC).[13]

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22 Date of Revision

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Starch, Pregelatinized

1 Nonproprietary Names

BP: Pregelatinised Starch

PhEur: Starch, Pregelatinised

USP-NF: Pregelatinized Starch

2 Synonyms

Amylum pregelificatum; compressible starch; *C*PharmGel*; *Instastarch*; *Lycatab C*; *Lycatab PGS*; *Merigel*; *National 78-1551*; *Pharma-Gel*; *Prejel*; *Sepistab ST200*; *Spress B820*; *Starch 1500 G*; *Tablitz*; *Unipure LD*; *Unipure WG220*.

3 Chemical Name and CAS Registry Number

Pregelatinized starch [9005-25-8]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ where n = 300–1000.

Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules. Both fully and partially pregelatinized grades are commercially available. Partial pregelatinization renders the starch flowable and directly compressible. Full pregelatinization produces a cold-water soluble starch that can be used as a wet granulation binder. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch. The USP32–NF27 does not specify the botanical origin of the original starch, but the PhEur 6.3 specifies that pregelatinized starch is obtained from maize (corn), potato, or rice starch. *See also* Starch and Section 13. Normally the fully pregelatinized starch contains 20–30% amylose and the rest amylopectin, which is about the same ratio (1 : 3) as for the partially pregelatinized form. There are ways to increase the amylose portion.[1]

5 Structural Formula

See Starch.

6 Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Partially pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent,[2,3] and disintegrant.[4]

In comparison to starch, partially pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry-compression or direct compression processes.[5–15] In such processes, pregelatinized starch is self-lubricating. However, when it is used with other excipients it may be necessary to add a lubricant to a formulation. Although magnesium stearate 0.25% w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution. Therefore, stearic acid is generally the preferred lubricant with pregelatinized starch.[16]

Partially pregelatinized starch is used in oral dry powder hard capsule formulations.

Both partially and fully pregelatinized starch may also be used in wet granulation processes.[17] *See* Table I.

Fully pregelatinized starches can be used to make soft capsules, shells, and coatings as well as binders in tablets.

Table I: Uses of pregelatinized starch.

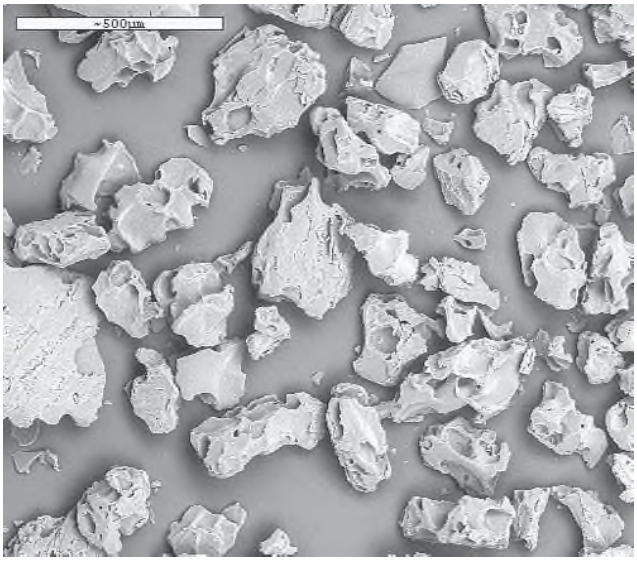
Use	Concentration (%)
Diluent (hard gelatin capsules)	5–75
Tablet binder (direct compression)	5–20
Tablet binder (wet granulation)	5–10
Tablet disintegrant	5–10

8 Description

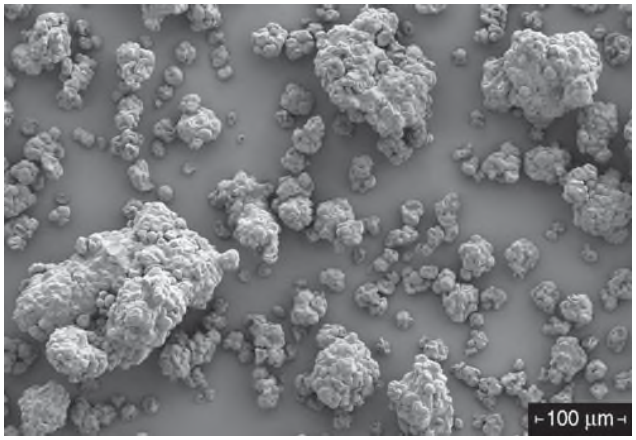
Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Examination of fully pregelatinized starch as a slurry in cold water, under a polarizing microscope, reveals no significant ungelatinized granules, i.e. no 'maltese crosses' characteristic of the starch birefringence pattern. Examination of samples suspended in glycerin shows characteristic forms depending upon the method of drying used during manufacture: either irregular chunks from drum drying or thin plates. Partially pregelatinized starch (e.g. *Starch 1500G* and *Sepistab ST200*) show retention of birefringence patterns typical of unmodified starch granules.

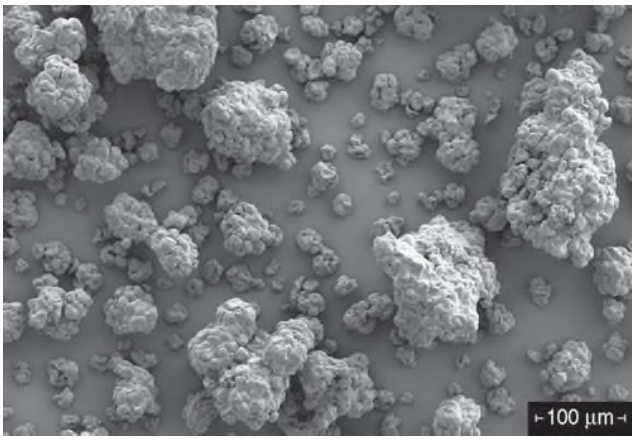
SEM 1: Excipient: *Lycatab PGS*; manufacturer: Roquette Frères.



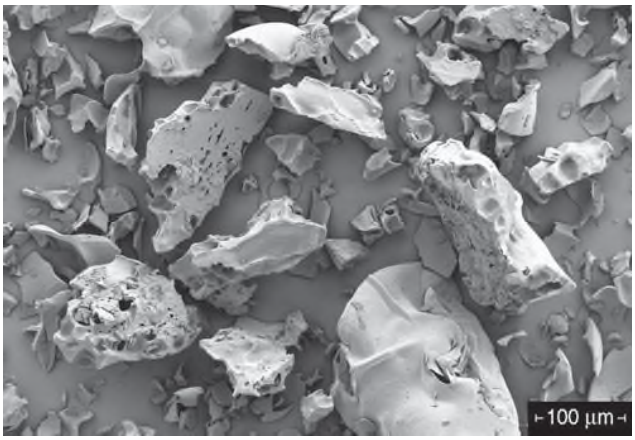
SEM 2: Excipient: pregelatinized starch; manufacturer: Cargill; magnification: 200×; voltage: 3 kV.



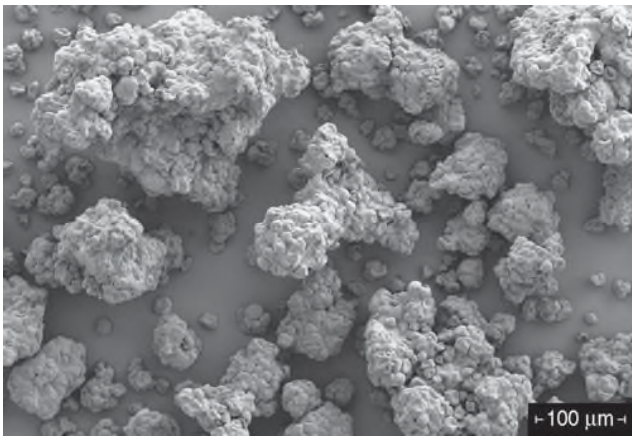
SEM 3: Excipient: pregelatinized starch; manufacturer: Cargill; magnification: 200×; voltage: 3 kV.



SEM 4: Excipient: pregelatinized starch; manufacturer: Cargill; magnification: 200×; voltage: 3 kV.



SEM 5: Excipient: pregelatinized starch; manufacturer: Cargill; magnification 200×; voltage: 3 kV.



9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

10 Typical Properties

Acidity/alkalinity pH = 4.5–7.0 for a 10% w/v aqueous dispersion.

Angle of repose 40.7° [6]

Density (bulk) 0.586 g/cm^3

Table II: Pharmacopeial specifications for pregelatinized starch.

Test	PhEur 6.3	USP32–NF27
Identification	+	+
Characters	+	–
pH (10% w/v slurry)	4.5–7.0	4.5–7.0
Iron	⩽20 ppm	⩽0.002%
Oxidizing substances	+	+
Sulfur dioxide	⩽50 ppm	⩽0.008%
Microbial limits	+	+
Loss on drying	⩽15.0%	⩽14.0%
Residue on ignition	–	⩽0.5%
Foreign matter	+	–
Sulfated ash	⩽0.6%	–

Density (tapped) 0.879 g/cm^3
Density (true) 1.516 g/cm^3
Flowability 18–23% (Carr compressibility index)[18]
Moisture content Pregelatinized maize starch is hygroscopic.[15,19,20] *See also* Figure 1.
NIR spectra *see* Figures 2 and 3.
Particle size distribution 30–150 µm, median diameter 52 µm. For partially pregelatinized starch, greater than 90% through a US #100 mesh (149 µm); and less than 0.5% retained on a US #40 mesh (420 µm).
Solubility Practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Pastes can be prepared by sifting the pregelatinized starch into stirred, cold water. Cold-water-soluble matter for partially pregelatinized starch is 10–20%.
Specific surface area

0.26 m^2/g (Colorcon);

0.18–0.28 m^2/g (Roquette).

Viscosity (dynamic) 8–10 mPa s (8–10 cP) for a 2% w/v aqueous dispersion at 25°C.

11 Stability and Storage Conditions

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Food-grade pregelatinized starches are prepared by heating an aqueous slurry containing up to 42% w/w of starch at 62–72°C. Chemical additives that may be included in the slurry are gelatinization aids (salts or bases) and surfactants, added to control rehydration or minimize stickiness during drying. After heating, the slurry may be spray-dried, roll-dried, extruded, or drum-dried. In the last case, the dried material may be processed to produce a desired particle size range.

Pharmaceutical grades of fully pregelatinized starch use no additives and are prepared by spreading an aqueous suspension of ungelatinized starch on hot drums where gelatinization and subsequent drying take place. Partially pregelatinized starch is produced by subjecting moistened starch to mechanical pressure. The resultant material is ground and the moisture content is adjusted to specifications.

14 Safety

Pregelatinized starch and starch are widely used in oral solid-dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of large amounts of pregelatinized starch may be harmful.

See Starch for further information.

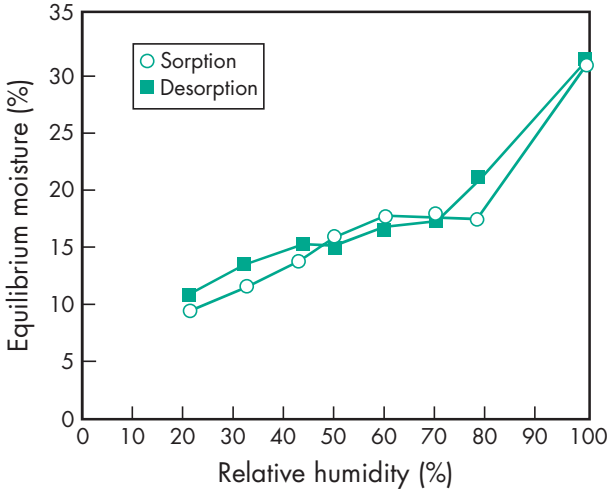


Figure 1: Pregelatinized starch sorption–desorption isotherm.

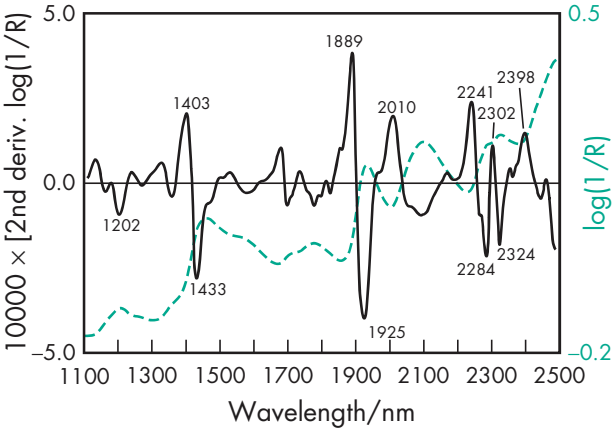


Figure 2: Near-infrared spectrum of pregelatinized maize starch measured by reflectance.

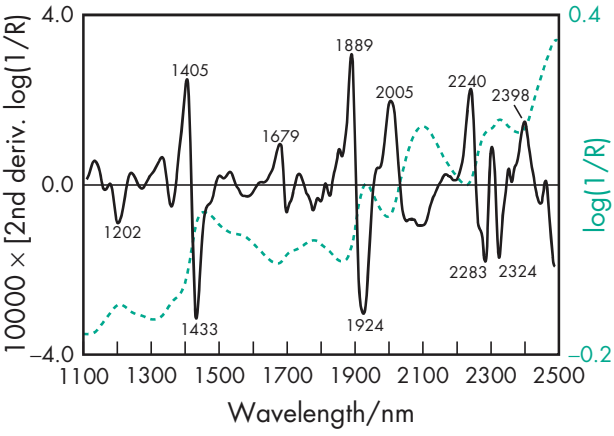


Figure 3: Near-infrared spectrum of pregelatinized rice starch measured by reflectance.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

S

In the UK, the long-term (8-hour TWA) workplace exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.[21]

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (oral capsules, suspensions, and tablets; vaginal preparations). Included in non-parenteral medicines licensed in the UK.

17 Related Substances

Corn starch and pregelatinized starch; starch; starch, sterilizable maize.

18 Comments

Pregelatinized starch is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

The USP32–NF27 also lists pregelatinized modified starch. A low-moisture grade of pregelatinized starch, *Starch 1500 LM* (Colorcon), containing less than 7% of water, specifically intended for use as a diluent in capsule formulations is commercially available.[16]

Sepistab ST200 is described as an agglomerate of starch granules consisting of native and pregelatinized corn starch.[22] Compression characteristics of pregelatinized starches from sorghum and plantain have been evaluated against traditional corn-based products.[23]

StarCap 1500 (Colorcon) is a coprocessed mixture of pregelatinized starch and corn starch promoted for use in dry-powder, hard-capsule fillings; *see* Corn Starch and Pregelatinized Starch.

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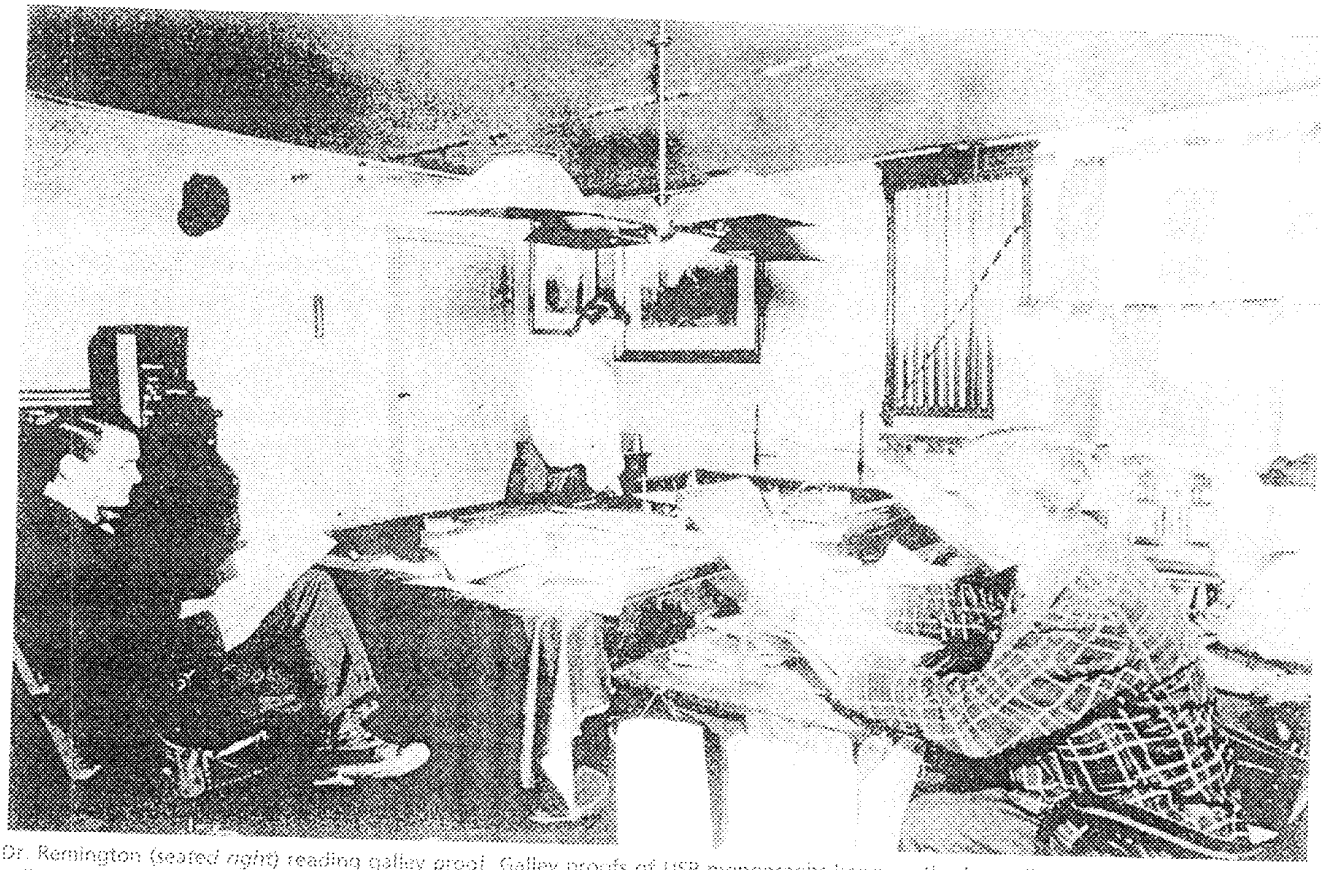

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Edwin T Sugita, PhD / Professor and Chairman, Pharmaceutics Department, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia. Coauthor of Chapter 11, *Pharmaceutical Calculations,* and Chapter 18, *Tonicity, Osmoticity, Osmolality, and Osmolarity.*

Bonnie L Svarstad, PhD / William S Apple Professor of Social and Administrative Pharmacy, School of Pharmacy, University of Wisconsin—Madison. Coauthor of Chapter 113, *The Patient: Behavioral Determinants.*

Craig K Svensson, PharmD, PhD / Professor, Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, Wayne State University. Coauthor of Chapter 58, *Basic Pharmacokinetics.*

James Swarbrick, PhD / Vice President for Research and Development, Applied Analytical Industries, Inc. Coauthor of Chapter 22, *Coarse Dispersions.*

Anthony R Temple, MD / Executive Director, Medical Affairs, McNeil Consumer Products Co; Adjunct Associate Professor, Department of Pediatrics, University of Pennsylvania School of Medicine; Lecturer, Philadelphia College of Pharmacy. Coauthor of Chapter 99, *Poison Control.*

Joseph Thomas III, PhD / Associate Professor of Pharmacy Administration, School of Pharmacy and Pharmacal Sciences, Purdue University. Author of Chapter 94, *Community Pharmacy Economics and Management.*

John P Tischio, PhD / Independent Consultant, Pharmaceutical Consulting Services, Manasquan, NJ. Author of Chapter 62, *Pharmacogenetics.*

Keith G Tolman, MD / Professor, Division of Gastroenterology, School of Medicine, University of Utah. Coauthor of Chapter 56, *Diseases: Manifestations and Pathophysiology* and Chapter 66, *Gastrointestinal and Liver Drugs.*

Salvatore J Turco, PharmD, FASHP / Professor of Pharmacy, Temple University School of Pharmacy. Author of Chapter 42, *Intravenous Admixtures.*

Elizabeth B Vadas / Senior Director, Pharmaceutical Research and Development, Merck Frosst Canada, Inc, Point Claire, Darval, Quebec. Author Chapter 52, *Stability of Pharmaceutical Products.*

Ernestine Vanderveen, PhD / National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, Maryland.

John E Vandervenn, PhD / Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC.

Vincent S Venturella, PhD / Director, Pharmaceutical Consulting, Ventura Associates, Wayne, NJ. Author of Chapter 26, *Natural Products.*

Jesse C Vivian, PhD, JD / Professor of Pharmacy Law, Department of Pharmacy Practice, Wayne State University. Coauthor of Chapter 90, *Laws Governing Pharmacy.*

Lane J Wallace, PhD / Professor of Pharmacology, College of Pharmacy, The Ohio State University. Author of Chapter 82, *Psychopharmacologic Agents.*

Maria L Webb, PhD / Director, Biology, Pharmacopeia, Princeton, NJ. Author of Chapter 10, *Research.*

Donna S West, PhD, FACA / University of Mississippi. Coauthor of Chapter 4, *The Practice of Community Pharmacy.*

Timothy S Wiedmann, PhD / Assistant Professor, College of Pharmacy, University of Minnesota. Author of Chapter 15, *Thermodynamics.*

Rodney J Wigent, PhD / Associate Professor of Chemistry, Research Associate, Professor of Pharmaceutics, University of the Sciences in Philadelphia. Author of Chapter 19, *Chemical Kinetics.*

Olivia B Wood, RD, MPh / Associate Professor of Foods and Nutrition, School of Consumer and Family Sciences, Purdue University. Author of Chapter 100, *Nutrition in Pharmacy Practice.*

Alisa Wright, BS, MS / Business Affairs Manager, Cook Pharmaceutical Solutions. Coauthor of Chapter 95, *Product Recalls and Withdrawals.*

Barbara J Zarowitz, PharmD, FCCP, BCPS / Vice President, Pharmacy Care Manager, Henry Ford Health System. Coauthor of Chapter 117, *Health-Care Delivery Systems and Interdisciplinary Care.*

Gilbert L Zink, PhD / Associate Professor of Biology, Department of Biological Sciences, University of the Sciences in Philadelphia. Author of Chapter 60, *Principles of Immunology.*

GLYCERYL MONOSTEARATE—page 1036.

HYDROXYETHYL CELLULOSE

Cellulose, 2-hydroxyethyl ether; Cellosize; Natrosol

Cellulose hydroxyethyl ether 9004-62-0.

Preparation—Cellulose is treated with NaOH and then reacted with ethylene oxide.

Description—White, odorless, tasteless, free-flowing powder; softens at about 137°; refractive index (2% solution) about 1.336; pH about 7; solutions are nonionic.

Solubility—Dissolves readily in cold or hot water to give clear, smooth, viscous solutions; partially soluble in acetic acid; insoluble in most organic solvents.

Uses—Resembles carboxymethylcellulose sodium in that it is a cellulose ether, but differs in being nonionic, and hence, its solutions are unaffected by cations. It is used pharmaceutically as a thickener, protective colloid, binder, stabilizer, and suspending agent in emulsions, jellies and ointments, lotions, ophthalmic solutions, suppositories, and tablets.

HYDROXYPROPYL CELLULOSE

Cellulose, 2-hydroxypropyl ether; Klucel

Cellulose hydroxypropyl ether [9004-64-2].

Preparation—After treating with NaOH, cellulose is reacted with propylene oxide at elevated temperature and pressure.

Description—Off-white, odorless, tasteless powder; softens at 130°; burns out completely about 475° in N_2 or O_2; refractive index (2% solution) about 1.337; pH (aqueous solution) 5 to 8.5; solutions are nonionic.

Solubility—Soluble in water below 40° (insoluble above 45°); soluble in many polar organic solvents.

Uses—A broad combination of properties useful in a variety of industries. It is used pharmaceutically as a binder, granulation agent, and film-coater in the manufacture of tablets; an alcohol-soluble thickener and suspending agent for elixirs and lotions; and a stabilizer for emulsions.

HYDROXYPROPYL METHYLCELLULOSE

Cellulose, 2-hydroxypropyl methyl ether

Cellulose hydroxypropyl methyl ether [9004-65-3], available in grades containing 16.5 to 30.0% of methoxy and 4.0 to 32.0% of hydroxypropoxy groups, and thus in viscosity and thermal gelation temperatures of solutions of specified concentration.

Preparation—The appropriate grade of methylcellulose (see below) is treated with NaOH and reacted with propylene oxide at elevated temperature and pressure for a reaction time sufficient to produce the desired degree of attachment of methyl and hydroxypropyl groups by ether linkages to the anhydroglucose rings of cellulose.

Description—White to slightly off-white, fibrous or granular, free-flowing powder.

Solubility—Swells in water and produces a clear to opalescent, viscous, colloidal mixture; undergoes reversible transformation from sol to gel on heating and cooling, respectively. Insoluble in anhydrous alcohol, ether, or chloroform.

Uses—A protective colloid that is useful as a dispersing and thickening agent, and in ophthalmic solutions to provide the demulcent action and viscous properties essential for contact-lens use and in *artificial-tear* formulations. See *Hydroxypropyl Methylcellulose Ophthalmic Solution* (page 1204).

LANOLIN, ANHYDROUS—page 1035.

METHYLCELLULOSE

Cellulose, methyl ether; Methocel

Cellulose methyl ether [9004-67-5]; a methyl ether of cellulose containing 27.5 to 31.5% of methoxy groups.

Preparation—By the reaction of methyl chloride or of dimethyl sulfate on cellulose dissolved in sodium hydroxide. The cellulose methyl ether so formed is coagulated by adding methanol or other suitable agent and centrifuged. Since cellulose has 3 hydroxyl groups/glucose residue, several methylcelluloses can be made that vary in, among other properties, solubility and viscosity. Types useful for pharmaceutical application contain from 1 to 2 methoxy radicals/glucose residue.

Description—White, fibrous powder or granules; aqueous suspensions neutral to litmus; stable to alkalies and dilute acids.

Solubility—Insoluble in ether, alcohol, or chloroform; soluble in glacial acetic acid or in a mixture of equal parts of alcohol and chloroform; swells in water, producing a clear to opalescent, viscous colloidal solution; insoluble in hot water and saturated salt solutions; salts of minerals, acids, and particularly polybasic acids, phenols, and tannins coagulate its solutions, but this can be prevented by the addition of alcohol or of glycol diacetate.

Uses—A synthetic substitute for natural gums that has both pharmaceutic and therapeutic applications. Pharmaceutically, it is used as a *dispersing, thickening, emulsifying, sizing,* and *coating agent.* It is an ingredient of many nose drops, eye preparations, burn medications, cosmetics, tooth pastes, liquid dentifrices, hair fixatives, creams, and lotions. It functions as a protective colloid for many types of dispersed substances and is an effective stabilizer for oil-in-water emulsions.

Therapeutically, it is used as a *bulk laxative* in the treatment of *chronic constipation.* Taken with 1 or 2 glassfuls of water, it forms a colloidal solution in the upper alimentary tract; this solution loses water in the colon, forming a gel that increases the bulk and softness of the stool. The gel is bland, demulcent, and nonirritating to the GI tract. Once a normal stool develops, the dose should be reduced to a level adequate for maintenance of good function. Although it takes up water from the GI tract quite readily, methylcellulose tablets have caused fecal impaction and intestinal obstruction when taken with a limited amount of water. It also is used as a topical ophthalmic protectant, in the form of 0.5 to 1% solution serving as artificial tears or a contact-lens solution applied to the conjunctiva, 0.05 to 0.1 mL at a time, 3 or 4 times a day as needed.

OLEYL ALCOHOL

9-Octadecen-1-ol, (*Z*)-, Aldol 85

(*Z*)-9-Octadecen-1-ol [143-28-2] $C_{18}H_{36}O$ (268.48); a mixture of unsaturated and saturated high-molecular-weight fatty alcohols consisting chiefly of oleyl alcohol.

Preparation—One method reacts ethyl oleate with absolute ethanol and metallic sodium (*Org Syn Coll III:* 673, 1955).

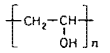
Description—Clear, colorless to light yellow, oily liquid; faint characteristic odor and bland taste; iodine value between 85 and 90; hydroxyl value between 205 and 215.

Solubility—Soluble in alcohol, ether, isopropyl alcohol, or light mineral oil; insoluble in water.

Uses—A *pharmaceutic aid* (emulsifying agent or emollient).

POLYVINYL ALCOHOL

Ethenol, homopolymer



Vinyl alcohol polymer [9002-89-5] $(C_2H_4O)_n$.

Preparation—Polyvinyl acetate is approximately 88% hydrolyzed in a methanol-methyl acetate solution using either mineral acid or alkali as a catalyst.

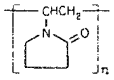
Description—White to cream-colored powder or granules; odorless.

Solubility—Freely soluble in water; solution effected more rapidly at somewhat elevated temperatures.

Uses—A *suspending agent* and *emulsifier,* either with or without the aid of a surfactant. It commonly is employed as a lubricant and protectant in various ophthalmic preparations, such as decongestants, artificial tears, and contact-lens products (see page 832).

POVIDONE

2-Pyrrolidinone, 1-ethenyl-, homopolymer; Polyvinylpyrrolidone; PVP



1-Vinyl-2-pyrrolidinone polymer [9003-39-8] $(C_6H_9NO)_n$; a synthetic polymer consisting of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. It is produced commercially as a series of products having mean molecular weights ranging from about 10,000 to about 700,000. The viscosity of solutions containing 10% or less is essentially the same as that of water; solutions more concentrated than 10% become more

EXHIBIT 5

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

5514 7590 12/10/2015

FITZPATRICK CELLA HARPER & SCINTO
1290 Avenue of the Americas
NEW YORK, NY 10104-3800

EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 12/10/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/942,646	11/09/2010	Glen Gary LAWRENCE	03858.001100.1	2069

TITLE OF INVENTION: RAPID DISSOLUTION FORMULATION OF A CALCIUM RECEPTOR-ACTIVE COMPOUND

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	03/10/2016

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

5514 7590 12/10/2015
FITZPATRICK CELLA HARPER & SCINTO
1290 Avenue of the Americas
NEW YORK, NY 10104-3800

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/942,646	11/09/2010	Glen Gary LAWRENCE	03858.001100.1	2069

TITLE OF INVENTION: RAPID DISSOLUTION FORMULATION OF A CALCIUM RECEPTOR-ACTIVE COMPOUND

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	03/10/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
SAMALA, JAGADISHWAR RAO	1618	514-654000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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5514 7590 12/10/2015

FITZPATRICK CELLA HARPER & SCINTO
1290 Avenue of the Americas
NEW YORK, NY 10104-3800

EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 12/10/2015

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 12/942,646	Applicant(s) LAWRENCE ET AL.	
	Examiner JAGADISHWAR SAMALA	Art Unit 1618	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *12/01/2015*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *2-5,7,9-20 and 23-28*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 11/13/2015
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *12/02/2015* .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J. S./ Examiner, Art Unit 1618	/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

- Receipt is acknowledged of Applicant's Amendment filed on 12/01/2015.
- Claims 2-5, 7, 9-10, 13, 19-20 and 23-24 have been amended.
- Claims 25-28 have been added.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 11/13/2015 has been entered.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Alicia Russo on 12/02/2015.

The application has been amended as follows:

Beginning of claim 25, delete "previously presented" and insert ---New---

Allowable Subject Matter

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 11/13/2015 was filed after the mailing date of the Notice of Allowance on 08/18/2015. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Please see attached copy of Form PTO/SB/08a.

The references from this Information Disclosure Statement were considered but are not deemed to be pertinent to the claimed invention. These documents relate to sustained release oral dosage forms and formulations for medicinal agents in general relevant to pharmaceutical science. However, claimed compositions are distinguished from the closet prior art by incorporating precise amounts of calcium receptor-active compound (cinacalcet HCl), the nature of the excipients and their respective combinations. The pharmaceutical composition provides unique dissolution profile (i.e., good bioavailability/rapid dissolution) of cinacalcet HCl (which is sparingly soluble at physiological intestinal pH in the stomach and the duodenum) which comprises from

about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test. Therefore, the claimed invention is still considered novel and patentably distinct.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAGADISHWAR SAMALA whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. S./
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Examiner-Initiated Interview Summary	**Application No.** 12/942,646	**Applicant(s)** LAWRENCE ET AL.	
	Examiner JAGADISHWAR SAMALA	**Art Unit** 1618	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JAGADISHWAR SAMALA*. (3)_____.

(2) *Alicia A Russo.*. (4)_____.

Date of Interview: *12/02/2015*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *Pending*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussed with applicants' representative:
Amendment to the claims and addition of new claims as detailed in Examiner's Amendment. Applicants' representative gave an overview of the instant invention with emphasis on good bioavailability/rapid dissolution of cinacalcet HCl.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/J. S./ Examiner, Art Unit 1618	

EXHIBIT 6

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

5514 7590 08/18/2015
FITZPATRICK CELLA HARPER & SCINTO
1290 Avenue of the Americas
NEW YORK, NY 10104-3800

EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 08/18/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/942,646	11/09/2010	Glen Gary LAWRENCE	03858.001100.1	2069

TITLE OF INVENTION: RAPID DISSOLUTION FORMULATION OF A CALCIUM RECEPTOR-ACTIVE COMPOUND

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	11/18/2015

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

5514 7590 08/18/2015
FITZPATRICK CELLA HARPER & SCINTO
1290 Avenue of the Americas
NEW YORK, NY 10104-3800

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/942,646	11/09/2010	Glen Gary LAWRENCE	03858.001100.1	2069

TITLE OF INVENTION: RAPID DISSOLUTION FORMULATION OF A CALCIUM RECEPTOR-ACTIVE COMPOUND

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	11/18/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
SAMALA, JAGADISHWAR RAO	1618	514-654000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/942,646	11/09/2010	Glen Gary LAWRENCE	03858.001100.1	2069

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1290 Avenue of the Americas
NEW YORK, NY 10104-3800

EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 08/18/2015

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 12/942,646	Applicant(s) LAWRENCE ET AL.	
	Examiner JAGADISHWAR SAMALA	Art Unit 1618	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *06/23/2015*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *2-5,7,9-20 and 23-28*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 06/23/2015
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4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J. S./ Examiner, Art Unit 1618	/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618

DETAILED ACTION

Allowable Subject Matter

The following is an examiner's statement of reasons for allowance:

The information disclosure statement (IDS) submitted on 06/23/2015 was filed after the mailing date of the Notice of Allowance on 03/25/2015. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Please see attached copy of Form PTO/SB/08a.

The references from this Information Disclosure Statement were considered but are not deemed to be pertinent to the claimed invention. These documents relate to oppositions filed in a related EP Patent No. EP-B-1 663 182. However, claimed compositions are distinguished from the closet prior art by the amount of cinacalcet HCl, the nature of the excipients and their respective amounts. The pharmaceutical composition provided good bioavailability/rapid dissolution of cinacalcet HCl (which is sparingly soluble at physiological intestinal pH in the stomach and the duodenum) can at all be provided by combining cinacalcet HCl with a binder and diluent in the respective amounts as defined in claim 1. Therefore, the claimed invention is still considered novel and patentably distinct.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination

under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 06/23/2015 has been entered.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAGADISHWAR SAMALA whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service

EXHIBIT 7

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

5514 7590 04/06/2016

FITZPATRICK CELLA HARPER & SCINTO
1290 Avenue of the Americas
NEW YORK, NY 10104-3800

EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 04/06/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/942,646	11/09/2010	Glen Gary LAWRENCE	03858.001100.1	2069

TITLE OF INVENTION: RAPID DISSOLUTION FORMULATION OF A CALCIUM RECEPTOR-ACTIVE COMPOUND

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	07/06/2016

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

5514 7590 04/06/2016
FITZPATRICK CELLA HARPER & SCINTO
1290 Avenue of the Americas
NEW YORK, NY 10104-3800

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/942,646	11/09/2010	Glen Gary LAWRENCE	03858.001100.1	2069

TITLE OF INVENTION: RAPID DISSOLUTION FORMULATION OF A CALCIUM RECEPTOR-ACTIVE COMPOUND

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	07/06/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
SAMALA, JAGADISHWAR RAO	1618	514-654000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/942,646	11/09/2010	Glen Gary LAWRENCE	03858.001100.1	2069

5514 7590 04/06/2016

FITZPATRICK CELLA HARPER & SCINTO
1290 Avenue of the Americas
NEW YORK, NY 10104-3800

EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 04/06/2016

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 12/942,646	Applicant(s) LAWRENCE ET AL.	
	Examiner JAGADISHWAR SAMALA	Art Unit 1618	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *03/08/2016*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *2-5,7,9-20 and 23-28*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 03/08/2016
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J. S./ Examiner, Art Unit 1618	/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

- Receipt is acknowledged of Applicant's Request for Continued Examination filed on 03/08/2016.
- Claims 2-5, 7, 9-20, 23-28 are pending in this application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 03/08/2016 has been entered.

Allowable Subject Matter

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 03/08/2016 was filed after the mailing date of the Notice of Allowance on 12/10/2015. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure

statement is being considered by the examiner. Please see attached copy of Form PTO/SB/08a.

The references from this Information Disclosure Statement were considered but are not deemed to be pertinent to the claimed invention. These documents relate to sustained release oral dosage forms and formulations for medicinal agents in general relevant to pharmaceutical science (Handbook of Pharmaceutical Excipients and Remington: The Science and Practice of Pharmacy). However, claimed compositions are distinguished from the closet prior art by incorporating precise amounts of calcium receptor-active compound (cinacalcet HCl), the nature of the excipients and their respective combinations. The pharmaceutical composition provides unique dissolution profile (i.e., good bioavailability/rapid dissolution) of cinacalcet HCl (which is sparingly soluble at physiological intestinal pH in the stomach and the duodenum) which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test. Therefore, the claimed invention is still considered novel and patentably distinct.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAGADISHWAR SAMALA whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. S./
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

CERTIFICATE OF SERVICE

I hereby certify that on June 28, 2019, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on June 28, 2019, upon the following in the manner indicated:

Benjamin J. Schladweiler, Esquire — *VIA ELECTRONIC MAIL*
GREENBERG TRAURIG, LLP
The Nemours Building
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Wilmington, DE 19801
Attorneys for Defendant Accord Healthcare, Inc.

Aaron F. Barkoff, Esquire — *VIA ELECTRONIC MAIL*
Alejandro Menchaca, Esquire
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500 West Madison Street, 34th Floor
Chicago, IL 60661
Attorneys for Defendant Accord Healthcare, Inc.

/s/ Jack B. Blumenfeld

Jack B. Blumenfeld (#1014)